IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

NIPPON SHINYAKU CO., LTD., Plaintiff, v. SAREPTA THERAPEUTICS, INC., Defendant.	)	C.A. No. 21-1015 (GBW)
SAREPTA THERAPEUTICS, INC., Defendant and Counter-Plaintiff, v. NIPPON SHINYAKU CO., LTD. and NS PHARMA, INC. Plaintiff and Counter-Defendants.	)	

JOINT CLAIM CONSTRUCTION BRIEF
FOR THE WILTON/UWA PATENTS

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March 20, 2023

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TABLE OF ABBREVIATIONS

Abbreviation	Description
’851 patent	U.S. Patent No. 9,994,851
’590 patent	U.S. Patent No. 10,227,590
’827 patent	U.S. Patent No. 10,266,827
’772 application	U.S. Application No. 15/274,772
Br.	Joint Claim Construction Brief
DMD	Duchenne muscular dystrophy
Italic	Emphasis added unless indicated otherwise
Ex. ____	Exhibit Number ____
Hastings Decl.	Declaration of Michelle L. Hastings, Ph.D. dated February 6, 2023
mRNA	messenger ribonucleic acid
NS	Plaintiffs/Counter-Defendants Nippon Shinyaku Co., Ltd. and NS Pharma, Inc.
Sarepta	Defendant/Counter-Plaintiff Sarepta Therapeutics, Inc.
Stein Decl.	Opening Declaration of Cy A. Stein, M.D., Ph.D. dated January 4, 2023
Stein Rep. Decl.	Reply Declaration of Cy A. Stein, M.D., Ph.D. dated February 27, 2023
Wilton Patents	U.S. Patent Nos. 9,994,851; 10,227,590; and 10,266,827

I. INTRODUCTION

A. Sarepta's Opening Position

1. Representative Claim

Sarepta has asserted claims 1-2 of the '851 patent, claims 1-2 of the '590 patent, and claims 1-2 of the '827 patent (the "Wilton patents") against NS. Stein Decl. ¶¶1, 18-24. The parties dispute the proper interpretation of the following claim terms: the "antisense oligonucleotide" phrase (highlighted in yellow) and three terms embedded within that phrase ("base sequence," "target region," and "exon 53 of the human dystrophin pre-mRNA" (each underlined)); the "annealing site" phrase (highlighted in purple); and the "thymine bases" phrase (highlighted in green). Claim 1 of the '851 patent is representative:

> 1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

Claim 1 of the '590 patent is similar but omits the "annealing site" phrase. Claim 1 of the '827 patent recites a method of treating Duchene muscular dystrophy ("DMD") using an antisense oligonucleotide having the features of claim 1 of the '590 patent.

2. Factual Background and Summary of Disputes

DMD is a devastating disease characterized by progressive muscular degeneration. Stein Decl. ¶¶33-35. The Wilton patents describe the ***first-ever*** FDA-approved treatments for DMD. Each of these treatments is an antisense oligonucleotide—a small string of nucleotides designed to target a region within genetic material derived from the human dystrophin gene known as a pre-

mRNA (made up of four types of bases, A, U, G, and C). The antisense oligonucleotide has bases that are complementary to those of its target region, and is capable of causing exclusion (i.e., "skipping") of a target exon when the pre-mRNA is further processed to produce dystrophin protein. Stein Decl. ¶¶36-41.

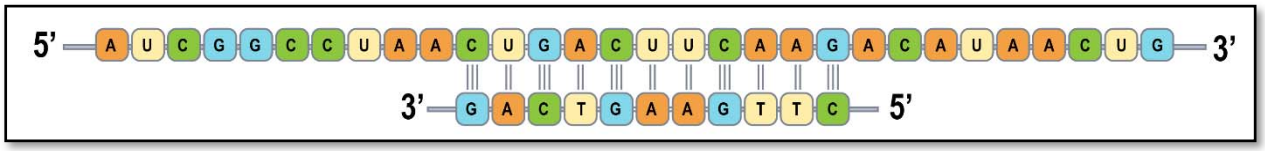


Figure 1. Complementary Base Sequences
(Stein Decl. ¶37)

The first approval, Sarepta's Exondys 51® (eteplirsen) therapy, occurred in 2016. While an important breakthrough, Exondys 51® targets exon 51 of the human dystrophin pre-mRNA, and consequently can only treat a subset of DMD patients having particular genetic mutations. But, as reflected in the asserted claims, the Wilton patents disclose additional antisense oligonucleotides targeting other exons of the human dystrophin pre-mRNA that can treat different sets of patients. This led to the approval of Sarepta's Vyondys 53® (golodirsen) product, which targets exon 53 of the human dystrophin pre-mRNA. NS's Viltepso® (viltolarsen) product, which similarly targets exon 53, was subsequently approved. Stein Decl. ¶¶42-43.

The claimed antisense oligonucleotides of the Wilton patents have three distinct characteristics. *First*, a defined length: each antisense oligonucleotide has 20 to 31 bases, which collectively form a base sequence. *Second*, complementarity: the base sequence of the antisense oligonucleotide is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA. *Third*, specified bases: the base sequence of the antisense oligonucleotide has (i) at least 12 consecutive bases derived from SEQ ID NO: 195 and (ii) thymine bases instead of uracil bases. For the '851 patent, the antisense oligonucleotide must also target a region defined by two annealing sites.

Sarepta's constructions interpret the claims from the perspective of a skilled artisan. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). The disputed terms, while technical, are routinely used in antisense oligonucleotide research—including by NS and the inventors of NS's own patents. The claims' meaning would have been clear to a skilled artisan, and Sarepta's constructions provide this ordinary meaning. In contrast, NS takes certain claim terms out of context, leading its constructions "astray." *See IGT v. Bally Gaming Int'l, Inc.*, 659 F.3d 1109, 1117 (Fed. Cir. 2011). For other terms, NS raises indefiniteness positions contradicting its prior positions. Regardless, these unsupported indefiniteness allegations should not be adjudicated without the benefit of a fully developed record.

B. Nippon's Responsive Position

The UWA Patents (or the "Wilton patents") do not—as Sarepta implies—claim specific, FDA-approved treatments for DMD. Instead, each asserted claim is broadly directed to a genus of "antisense oligonucleotide[s]" defined using a set of recited characteristics (*e.g.*, length and morpholino backbone chemistry) that purportedly induce exon 53 skipping.[1] The parties dispute the meaning of five discrete terms used throughout the claims:

- **Term 1a ("a base sequence"):** Does "base sequence" mean **any** sequence of bases, or is it limited only to sequences of bases that span an **entire** antisense oligonucleotide?
- **Term 1b ("a target region"):** Does "target region" refer to any portion of the pre-mRNA to which an oligonucleotide binds or does it specify a portion of the pre-mRNA having a physical or functional purpose?
- **Term 1c ("exon 53 of the human dystrophin protein"):** Does this refer to the wild-type or mutated forms of "the human dystrophin pre-mRNA"?

[1] The '827 Patent is directed to methods of using oligonucleotides.

- **Term 2 ("wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69)"):** Does this refer to a region that is in both annealing sites or in either annealing site?

- **Term 3 ("in which uracil bases are thymine bases"):** What preceding term does the phrase "uracil bases are thymine bases" modify—antisense oligonucleotide or SEQ ID No: 195?

NS's positions faithfully apply the principles set forth in Federal Circuit precedent, including *Phillips v. AWH Corp.*, by interpreting claim terms "in the context of the **entire** patent,"[2] including the surrounding claim language, specification, and prosecution history. 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). As discussed below, the intrinsic evidence mandates NS's proposed construction for Term 1a and demonstrates irreconcilable issues with the remaining terms that leave a person of ordinary skill in the art ("POSA") without reasonable certainty regarding the scope of the UWA Patents' claims. *See Nautilus, Inc. v. Biosig. Instruments, Inc.*, 572 U.S. 898, 910 (2014).

By contrast, Sarepta repeatedly ignores now-inconvenient claim language and specification disclosures, and impermissibly rewrites claims to render limitations superfluous and change their scope. Courts, however, "construe the claim as written, not as the patentees wish they had written it." *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374-75 (Fed. Cir. 2004). The Court should therefore adopt NS's proposed construction for Term 1a and find the UWA Patents invalid for indefiniteness due to Terms 1b, 1c, 2, and 3.

C. Sarepta's Reply Position

Claim language "must be construed in the context of the claim in which it appears." *IGT*, 659 F.3d at 1117. Instead of applying this principle, NS repeatedly assigns out-of-context meanings that a skilled artisan would not have considered reasonable.

[2] Emphasis is added throughout NS's briefing unless otherwise noted.

NS has also failed both to satisfy its burden of proving indefiniteness by clear and convincing evidence *and* to justify addressing it at this early stage of the case. While NS asserts that its indefiniteness theories "predominantly" rise and fall on the intrinsic evidence (Br. 13 n.4), the record belies that assertion—the parties have already served competing expert declarations (spanning over 300 paragraphs) relying on numerous exhibits. Addressing these issues now would deprive the Court of the benefit of ongoing discovery and the opportunity to assess expert credibility. *Otsuka Pharm. Co. v. Zenara Pharma Priv. Ltd.*, C.A. No. 19-1938-LPS, 2021 WL 3172017, at *4-5 (D. Del. July 27, 2021) (declining to rule on indefiniteness at the *Markman* stage).

II. DEFINITION OF A SKILLED ARTISAN

A. Sarepta's Opening Position

"[T]he words of a claim are generally given their ordinary and customary meaning," which is the meaning they would have to a skilled artisan at the time of the invention. *Phillips*, 415 F.3d at 1312-13. Here, a skilled artisan would have had a Ph.D. in chemistry, biochemistry, cell biology, genetics, molecular biology, or an equivalent, and several years of experience with antisense oligonucleotides for inducing exon skipping. Stein Decl. ¶¶25-26.

To assist the Court's understanding of the technical terms at issue, Sarepta submits the declaration of Cy A. Stein, M.D., Ph.D. *Id.* ¶¶2-13. Dr. Stein is a founder of the Oligonucleotide Therapeutics Society, recipient of its Lifetime Achievement Award in 2022, and the retired Emeritus Arthur and Rosalie Kaplan Professor and Chair of Medical Oncology and Experimental Therapeutics at City of Hope Medical Center. *Id.* He has decades of experience in designing and testing antisense oligonucleotides as potential therapies and has authored more than 230 peer-reviewed articles, book chapters, and reviews. *Id.*

B. Nippon's Responsive Position

NS proposes that a "POSA" would have an M.D., Ph.D. or lower degree with expertise in molecular biology, biochemistry or a related area, and experience with neuromuscular or genetic diseases and/or designing and testing antisense oligonucleotides for splice-site switching/exon skipping applications. As Dr. Michelle Hastings, Ph.D., a Professor at Rosalind Franklin University and the Chicago School of Medicine, explains, Sarepta's proposed definition would exclude those with relevant experience having degrees such as an M.S., B.S./B.A., or M.D. (which makes little sense considering the '827 Patent requires administering an antisense oligonucleotide to a patient). Ex, 43 ¶¶19-21.

C. Sarepta's Reply Position

NS contends that individuals with an M.S., B.S./B.A., or M.D. could qualify as skilled artisans. Br. 6. Sarepta agrees that a medical doctor could qualify as a skilled artisan if she had several years of experience designing and using exon skipping antisense oligonucleotides and related therapies. Given the highly technical nature of the invention, however, a person with only a B.S./B.A. or M.S. degree would be unlikely to possess that knowledge and experience. Stein Rep. Decl. ¶¶1-6; *see* Stein Decl. ¶¶25-41. Notably, each inventor of the Wilton Patents has a Ph.D. *See Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1257 (Fed. Cir. 2007) (considering the inventors' educational level in defining a skilled artisan). Regardless, Sarepta's constructions conform to a skilled artisan's understanding under either party's definition

III. AGREED-UPON CONSTRUCTIONS

The parties have no agreed-upon constructions.

IV. DISPUTED CONSTRUCTIONS

A. Term 1 and Sub-Terms 1a, 1b, 1c

Term	Claim Language	Sarepta's Proposed Construction / Contention	NS's Proposed Construction / Contention
1	"antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA"	*Not indefinite* *No construction needed in light of inter alia, the intrinsic evidence and the knowledge of a person of ordinary skill in the art* To the extent construction is needed, Sarepta proposes that the phrase should be given its plain and ordinary meaning, i.e., "antisense oligonucleotide that has 20 to 31 bases, which collectively form a sequence that is 100% complementary to a segment of the pre-mRNA transcribed from exon 53 of the human dystrophin gene"	*Indefinite*; Or, in the alternative: "antisense oligonucleotide with 20 to 31 bases that includes any sequence of bases that is part of the antisense oligonucleotide that are 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA"
Sub-terms:		*Should be construed together as a complete phrase and if so, no construction needed in light of, inter alia, the intrinsic evidence and the knowledge of a person of ordinary skill in the art* To the extent construction is needed, Sarepta proposes that each phrase should be given its plain and ordinary meaning, i.e.:	
1a	"a base sequence"	"a linear sequence of bases"	"any sequence of bases that is part of the antisense oligonucleotide"
1b	"a target region"	"a segment of the pre-mRNA"	*Indefinite.*
1c	"exon 53 of the human dystrophin pre-mRNA"	"the pre-mRNA transcribed from exon 53 of the human dystrophin gene"	*Indefinite.*

1. Term 1: "antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA"

a. Sarepta's Opening Position

i. A Skilled Artisan Would Have Understood the Antisense Oligonucleotide Phrase When Read in Its Entirety

The antisense oligonucleotide phrase appears in each claim of the Wilton patents. Stein Decl. ¶¶44-45. Consistent with the intrinsic evidence and knowledge in the art, a skilled artisan would have read this phrase as a whole and understood it to convey that the bases of the antisense oligonucleotide collectively form a sequence ("base sequence") that is 100% complementary to a segment of the pre-mRNA ("target region") transcribed from exon 53 of the human dystrophin gene ("exon 53 of the human dystrophin pre-mRNA"). Given the phrase's plain and ordinary meaning to a skilled artisan, it does not need any construction.

The Wilton patents explain how an antisense oligonucleotide exerts its biological effects.[3] Stein Decl. ¶¶46-49, 27-40. Antisense oligonucleotides are "capable of binding to *specified dystrophin pre-mRNA targets*." Ex. 1 at 23:38-41. Each "target" is a segment of a pre-mRNA molecule (i.e., "target region"), which is transcribed from a gene of interest, in this case, the human dystrophin gene (i.e., "the human dystrophin pre-mRNA"). *Id.* at 24:61-25:11 (antisense oligonucleotides "capable of binding to *a selected target in the dystrophin pre-mRNA*"); *id.* at 24:48-60 ("target sites" can be identified based on a "gene" or the "mRNA *transcribed* [from] the gene"). In some cases, this "target" is present in an exon of the human dystrophin pre-mRNA. *Id.* at 23:24-27 (antisense oligonucleotides "*targeted* to nucleotide sequences . . . *in exons within pre-*

[3] Unless indicated otherwise, citations refer to the '851 patent as representative of the Wilton patents.

mRNA sequences"). As reflected in the claim language, "exon 53 of the human dystrophin pre-mRNA" is one such exon that can be targeted for exon skipping. *Id.* at 25:2-11, 4:47-49.

An antisense oligonucleotide is capable of binding to its target because the "sequences" of the antisense oligonucleotide and target are complementary, i.e., the bases of the antisense oligonucleotide can pair with their corresponding bases in the target. *Id.* at 25:18-38; Stein Decl. ¶¶50-51. Each "sequence" is composed of bases arranged in a linear fashion (i.e., "base sequence"). Stein Decl. ¶¶50-51. Table 1A of the Wilton patents, for example, describes exemplary antisense oligonucleotides. Ex. 1 at cols. 7-19. Each antisense oligonucleotide contains a string of bases composed from four bases—adenine (A), uracil (U) (or thymine (T) in case of morpholinos), guanine (G), and cytosine (C)—linearly arranged in a nucleotide sequence. *Id.* (column titled "NUCLEOTIDE SEQUENCE" in Table 1A). The specification defines the length of an antisense oligonucleotide by its number of bases and describes those bases collectively as a "sequence" or "base sequence." *Id.* at 23:62-24:3, 25:61-26:3.

The terminology used in the Wilton patents is consistent with how a skilled artisan would have described an antisense oligonucleotide targeting exon 53 of the human dystrophin pre-mRNA. Stein Decl. ¶¶46-56, 58. Dr. Stein, for example, has identified numerous prior art articles from both the inventors and independent researchers that use identical or nearly identical terms in discussing antisense oligonucleotides designed to cause skipping of an exon of the human dystrophin pre-mRNA. *E.g.*, Ex. 4 at S71 (2002 article from independent researchers discussing antisense oligonucleotides "targeting" sequences "within the DMD pre-mRNA"); Ex. 19 at 645, 651-52 (2002 article from the Wilton patent inventors explaining that antisense oligonucleotides are designed to "induce *targeted* removal of disease-causing *exons from pre-mRNA transcripts* during splicing" and identifying several "target sites" in an exon of interest). Even Dr. Takeda, a

named inventor of NS's patents, has used the same terminology. Ex. 28 at 94 (Dr. Takeda in 2007 explaining that "[e]xon skipping using *antisense oligonucleotides* (AO) *targets transcribed RNA molecules* to omit a nonsense mutation and restore a disrupted reading frame").

The same common usage of these technical terms is reflected in a Patent Office decision in a prior interference proceeding involving a related Wilton patent. Ex. 17 at 3 (the Board describing the claimed subject matter as "an oligonucleotide that includes *a nucleobase sequence* that is complementary to *a portion of a particular pre-mRNA exon*," in particular "*exon 53 of the pre-mRNA* associated with *the gene responsible for the formation of the protein dystrophin*"); Stein Decl. ¶57.

Rather than reading the claimed phrase as a whole in context, NS proposes that the Court should consider three embedded terms in isolation—"a base sequence," "a target region," and "exon 53 of the human dystrophin pre-mRNA." D.I. 144 at Exhibit B. But as the Federal Circuit has held, "claim language must be construed in the context of the claim in which it appears" because "[e]xtracting a single word from a claim divorced from the surrounding limitations can lead construction astray." *IGT*, 659 F.3d at 1117; *see ACTV, Inc. v. Walt Disney Co.*, 346 F.3d 1082, 1088 (Fed. Cir. 2003) ("While certain terms may be at the center of the claim construction debate, the context of the surrounding words of the claim . . . must be considered in determining the ordinary and customary meaning of those terms."). That is precisely the problem with NS's approach. NS's alternative construction of the overall phrase fares no better, as it simply substitutes the claim term "a base sequence" with its flawed construction without explaining what the remainder of the overall phrase means. *See infra* § IV.A.2.a; Stein Decl. ¶¶59-62.

Because a skilled artisan would have understood the antisense oligonucleotide phrase, no construction is necessary. Nevertheless, should the Court believe that the jury would benefit from

a construction, Sarepta's plain and ordinary construction is consistent with the intrinsic and extrinsic evidence.

ii. The Antisense Oligonucleotide Phrase Is Not Indefinite

NS argues that the antisense oligonucleotide phrase is indefinite because two embedded terms are not expressly defined in the specification: (i) "a target region" and (ii) "exon 53 of the human dystrophin pre-mRNA." Ex. 36 at 26. For the latter term, NS also asserts a purported lack of antecedent basis. *Id.*

NS has the burden of proving indefiniteness by clear and convincing evidence. *BASF Corp. v. Johnson Matthey Inc.*, 875 F.3d 1360, 1365 (Fed. Cir. 2017). Moreover, an express definition is not needed to satisfy the definiteness requirement. *Biosig Instruments, Inc. v. Nautilus, Inc.*, 783 F.3d 1374, 1382-84 (Fed. Cir. 2015) (holding that a claim term was definite notwithstanding the lack of an express definition in the specification); *Bancorp Servs., L.L.C. v. Hartford Life Ins. Co.*, 359 F.3d 1367, 1373 (Fed. Cir. 2004) ("[I]f the meaning of the term is fairly inferable from the patent, an express definition is not necessary."). A skilled artisan reading the Wilton patents would have understood that "exon 53 of the human dystrophin pre-mRNA" refers to the pre-mRNA transcribed from exon 53 of the human dystrophin gene. *See supra* § IV.A.1.a.i; Stein Decl. ¶¶63-64. A skilled artisan also would have understood that "a target region" refers to a segment of the pre-mRNA that the claimed antisense oligonucleotide is complementary to. Stein Decl. ¶¶63-64; *see also id.* ¶¶36-38.

The recitation of "the" in "exon 53 of the human dystrophin pre-mRNA" does not render the claim language indefinite because the claim apprises a skilled artisan of its scope. *In re Downing*, 754 F. App'x 988, 996 (Fed. Cir. 2018); *see Energizer Holdings, Inc. v. Int'l Trade Comm'n*, 435 F.3d 1366, 1370 (Fed. Cir. 2006) (definiteness of a claim term lacking antecedent basis "must be decided in context"). Here, the dystrophin gene was discovered nearly twenty years

before the Wilton patents were filed. Stein Decl. ¶65. The sequence of each exon (including exon 53) of the human dystrophin pre-mRNA was also known. *Id.* A skilled artisan understood the meaning of "exon 53 of the human dystrophin pre-mRNA." Indeed, a skilled artisan would have understood that the use of "the" in this context is appropriate since there is only *one* sequence, i.e., "the" sequence, associated with exon 53 of the human dystrophin pre-mRNA. *Id.*

Before this litigation, NS had no difficulty understanding these terms. Stein Decl. ¶66. During prosecution of one of its own patents, NS never questioned the Examiner's repeated use of the terms "target region" and "the dystrophin pre-mRNA." Ex. 21 at NS00000760 (NS summarizing the Examiner's obviousness rejection based on a "target region" within "the 53rd exon of the human dystrophin gene" described in the prior art). In fact, the claims of NS's U.S. Patent No. 9,708,361 refer to "*the* 53rd exon in the human dystrophin gene" with no antecedent basis. Ex. 29 at claim 1. NS's prior understanding of these terms highlights the litigation-driven nature of its indefiniteness challenges.

iii. The Court Should Defer Ruling on NS's Indefiniteness Contentions Until After Fact and Expert Discovery

Sarepta respectfully submits that the Court should defer ruling on NS's indefiniteness contentions until after the record has been more fully developed.

The disputed claim terms at issue are technical terms used in the specialized field of antisense oligonucleotide research. The definiteness of the claim language in this case turns on whether a skilled artisan, based on general knowledge in the art, would have been able to ascertain the meaning and scope of the claims with reasonable certainty. *See Dow Chem. Co. v. Nova Chems. Corp.*, 809 F.3d 1223, 1225 (Fed. Cir. 2015) (Moore, J., concurring) ("Appreciating what a skilled artisan knew at the time of the invention is pertinent to whether the claims are reasonably clear in their meaning and scope."). To address these highly technical issues, the Court here would

benefit from further evidentiary development. *See Verve, L.L.C. v. Crane Cams, Inc.*, 311 F.3d 1116, 1119-20 (Fed. Cir. 2002) (definiteness of a technical term can be supported by extrinsic evidence as "[p]atent disputes often raise close questions requiring refinement of technical definitions in light of particular facts"). Given the technical nature of the disputed claim terms and the likelihood that the meaning of those terms will be further elucidated during ongoing discovery in this case, it would be appropriate for the Court to decline to rule on indefiniteness at the *Markman* stage. *See, e.g.*, *Otsuka*, 2021 WL 3172017, at *4-5 (declining to rule on indefiniteness at the *Markman* stage in view of factual disputes over the understanding of a skilled artisan); *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, C.A. No. 16-7721-JLL, 2019 WL 1789463, at *4 (D.N.J. Apr. 24, 2019) (similarly declining to do so because, *inter alia*, discovery was ongoing).

b. Nippon's Responsive Position

i. Term 1 Should Not Be Construed in Its Entirety

Although the parties dispute particular issues implicated by Terms 1a, 1b, and 1c (shown above), and not the entirety of Term 1, Sarepta argues that the Court should construe the entirety of Term 1 in lieu of addressing those disputes directly.[4] This position is legally erroneous.

Sarepta's purported justification for its collective approach is that "claim language must be construed in the context of the claim in which it appears." Br. 10. However, one need not construe undisputed claim terms to consider the context they provide. While courts must resolve "actual dispute[s] regarding the proper scope of…claims," they "are not (and should not be) required to

[4] Because the indefiniteness issues raised here predominantly rise and fall on the intrinsic evidence, the Court should decide them during claim construction, as is routinely done. *See Interval Licensing LLC v. AOL, Inc.*, 766 F.3d 1364, 1368 (Fed. Cir. 2014) (reviewing on appeal indefiniteness finding made in district court's claim construction order).

construe *every* limitation present in a patent's asserted claims." *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co.*, 521 F. 3d 1351, 1362 (Fed. Cir. 2008); *see Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.").

By focusing on the "entire phrase" Sarepta glosses over its attempt to rewrite claim elements by omitting key limitations, including that the claimed antisense oligonucleotides "comprise" a "base sequence." As shown below, Sarepta's collective construction noticeably differs from both (1) the original claim language; and (2) Sarepta's individual constructions in that it **eliminates** the transitional phrase "comprising" and the language "consecutive bases of":

Claim Language	Sarepta's Individual Constructions	Sarepta's Collective Construction
"antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA"	"antisense oligonucleotide of 20 to 31 bases comprising [a linear sequence of bases] that is 100% complementary to consecutive bases of [a segment of the pre-mRNA transcribed from exon 53 of the human dystrophin gene]"	"antisense oligonucleotide that has 20 to 31 bases, which collectively form a sequence that is 100% complementary to a segment of the pre-mRNA transcribed from exon 53 of the human dystrophin gene"

Both omissions materially alter claim scope and deprive the disputed terms of their original context. As Dr. Hastings explains, eliminating "comprising" "changes the claim from meaning that the 'antisense oligonucleotide of 20 to 31 bases' **includes** a 'base sequence,' to meaning that the '20 to 31 bases' **is** the 'base sequence.'" Ex. 43 ¶85. Eliminating "consecutive bases of" impacts limitations because it "changes how the '100% complementary' limitation operates." *Id.* ¶86. "Instead of requiring complementarity to '**consecutive bases** of the target region' specifically, Sarepta's collective construction requires complementarity to the 'target region' generally." *Id.*

Sarepta's purported contextual justification for collectively construing Term 1 is contrary to its own analysis, which lacks any consideration of the surrounding context. Nowhere does Sarepta discuss the claim's grammatical structure, the importance of the phrase "comprising," or the influence of phrases like "consecutive bases of" on Term 1 overall. Instead, Sarepta's discussion for consolidated Term 1 focuses on everything but the claim language. *See* Br. 8-10 (discussing specification disclosures, Dr. Stein's declaration, and other ***extrinsic*** evidence).

The Court should reject Sarepta's attempt to re-write the claims and should consider the discrete interpretive issues implicated by Terms 1a, 1b, and 1c. However, if the Court decides to construe the entirety of Term 1, it should be held indefinite as a whole, or, if found definite, it should be construed as NS proposes to retain the original claims' context.[5]

c. Sarepta's Reply Position

Sarepta has explained why this phrase should be construed as a whole. Br. 8-11. In response, NS argues there is no need to construe certain undisputed terms to consider the context they provide. Br. 13-14. Sarepta is not seeking to do so. Rather, Sarepta proposes construing the entire phrase because it collectively conveys a plain meaning that would be apparent to a skilled artisan. Br. 8-11; *ACTV*, 346 F.3d at 1088 (the surrounding words of the claim must be considered in determining an ordinary and customary meaning).

NS incorrectly asserts that Sarepta's construction omits certain limitations—"comprising," "base sequence," and "consecutive bases of." Br. 14. Sarepta's construction identifies a "sequence" formed by the bases of the antisense oligonucleotide ("base sequence") that is 100% complementary to a segment of the pre-mRNA ("consecutive bases"). This construction does not

[5] While Sarepta's individual constructions are also wrong, they do not rewrite the claims as extensively as Sarepta's collective construction. Thus, should the Court disagree with NS and intend to adopt one of Sarepta's two proposals, it should adopt Sarepta's individual constructions.

exclude other elements present in the claimed antisense oligonucleotide, for example, backbone structures permitted by the "comprising" claim language. *See infra* § IV.A.2.c.i.(a); Stein Rep. Decl. ¶¶43-45.

NS's proposal to fragment this phrase into individual embedded terms should be rejected. Nevertheless, should the Court construe each term separately, Sarepta's constructions should be adopted for the reasons discussed below.

d. Nippon's Sur-reply Position

i. Sarepta's Collective Construction for Term 1 Impermissibly Re-writes the Claims

Sarepta argues that its collective construction does not omit "comprising" and "consecutive bases of," but its word choice demonstrates otherwise. Sarepta's collective construction literally re-writes the claims to materially alter claim scope and should be rejected.

Sarepta's arguments for Term 1 and 1a seek to avoid the consequences of the claim's "comprising" language. Sarepta concedes that "comprising" means that the claims' "named elements" are non-exclusive and that the claims generally permit "other elements." Br. 33. But instead of uniformly applying this meaning, Sarepta impermissibly picks-and-chooses what the claim permits ("chemical backbone and 5' cap"), and what it excludes (additional bases or "base sequences"). *Id.*

2. Terms 1a, 1b, and 1c: Embedded Terms: "a base sequence," "exon 53 of the human dystrophin pre-mRNA," and "a target region"

a. Sarepta's Opening Position

NS's proposal to parse the antisense oligonucleotide phrase into pieces is improper. *See supra* § IV.A.1.a.i. But to the extent that the Court considers these embedded terms separately, Sarepta's constructions reflect their meaning to a skilled artisan.

When read in context, a skilled artisan would have understood that the bases of each claimed antisense oligonucleotide collectively form "a base sequence," i.e., a linear sequence of bases. That base sequence must be 100% complementary to "a target region," i.e., a segment of the pre-mRNA. That pre-mRNA segment is in "exon 53 of the human dystrophin pre-mRNA," i.e., the pre-mRNA transcribed from exon 53 of the human dystrophin gene. These constructions conform to how the same or nearly identical terminology is used in the specification and the art. *See supra* § IV.A.1.a.i; Stein Decl. ¶67.

NS wrongly alleges that the terms "target region" and "exon 53 of the human dystrophin gene" are indefinite. They are not, as discussed above. *See supra* § IV.A.1.a.ii; Stein Decl. ¶70. NS construes the remaining term, "a base sequence," as "any sequence of bases that is part of the antisense oligonucleotide." By injecting "any" and "part" into the construction, NS implies that the claimed antisense oligonucleotide might contain bases that are *not* complementary to exon 53 of the human dystrophin pre-mRNA. But NS's interpretation is unsupported by the intrinsic evidence. Stein Decl. ¶¶68-69. Indeed, NS ignores the express claim limitation requiring the "base sequence" to be "100% complementary" to exon 53 of the human dystrophin pre-mRNA. NS's position is also inconsistent with the exemplary antisense oligonucleotides disclosed in the specification, which illustrate that the "base sequence" refers to ***all*** of the bases of the antisense oligonucleotide. *See supra* § IV.A.1.a.i; Ex. 1 at Table 1A.

b. Nippon's Responsive Position

i. Term 1a – "a base sequence"

Claim 1 of each UWA Patent recites "[a]n antisense oligonucleotide of 20 to 31 bases **comprising** *a base sequence* that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA." *See* Ex. 1, '851 Patent, cl. 1. Sarepta contends that "base sequence" is limited only to "a linear sequence of bases" that consist of ***all*** bases of the

"antisense oligonucleotide," rendering the "a base sequence" limitation meaningless.[6] Br. 8-11. NS, on the other hand, contends that "a base sequence" should carry its plain and ordinary meaning—that it includes any sequence of bases within the claimed antisense oligonucleotide. The Court should adopt NS's proposed construction because it comports with the intrinsic evidence.

(a) The Claim Language Mandates NS's Construction

The claims each recite an "antisense oligonucleotide of 20 to 31 bases **comprising** *a base sequence*" that has certain complementarity and "comprises at least 12 consecutive bases of…SEQ ID NO: 195," *id.*:

> **1**. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

'851 Patent, cl. 1. This surrounding claim language is critical to interpreting Term 1.

Because the claims recite "comprising" before "a base sequence," Federal Circuit law mandates NS's proposed construction. "'Comprising'…means that the named elements are essential, but other elements may be added and still form a construct within the scope of the claim." *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997); MPEP § 2111.03 (describing

[6] Sarepta's proposed construction for Term 1a individually ("a linear sequence of bases") does not capture the concept. As Dr. Hastings explains, "[a] sequence of bases can be 'linear' without spanning an entire antisense oligonucleotide, such that an 'antisense oligonucleotide…comprising a linear sequence of bases' would still…not exclude other bases or base sequences." Ex. 43 ¶44.

"comprising" as "synonymous with 'including'"). Thus, properly interpreted, the claims require that the "antisense oligonucleotide of 20 to 31 bases" **includes** "a base sequence" meeting the subsequently recited limitations. The element does not mean that the "antisense oligonucleotide" consists **only** of the recited "base sequence" and excludes other bases, as Sarepta asserts. *Cf. Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016) (using "consisting" "exclude[s] any elements…not specified in the claim").

The Federal Circuit has likewise "repeatedly emphasized that an indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising.'" *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (2000) (collecting cases); *see also Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342 (2008) (quoting same). Thus, properly interpreted, the claims should also allow the "antisense oligomer" to include "one or more" of the **recited** "base sequence" (*i.e.*, more than one sequence of bases that meet the additional claim limitations describing the "base sequence").

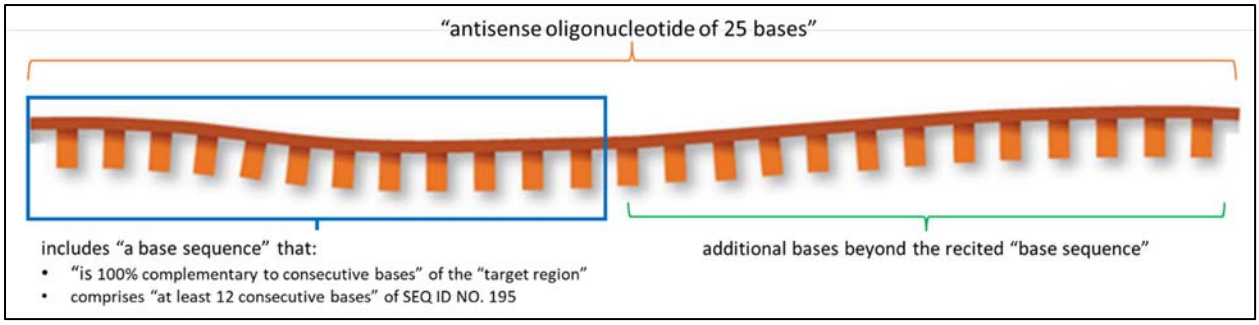
NS's proposed construction—which clarifies that "base sequence" encompasses "any sequence of bases that is part of the antisense oligonucleotide"—preserves both possibilities by reaffirming that the claimed "base sequence" need only be **included** in the antisense oligonucleotide, and it need not (though certainly could) span the entirety of the antisense oligonucleotide. By contrast, Sarepta's construction directly contradicts Federal Circuit law regarding the non-exclusive nature of "comprising." *See, e.g.*, *Genentech*, 112 F.3d at 501; *KCJ Corp.*, 223 F.3d at 1356. Under Sarepta's interpretation, each antisense oligonucleotide would have only **one** "base sequence"—the claimed "antisense oligonucleotide" could never have additional unrecited bases beyond the "base sequence," nor could it have "more" than one recited "base sequence."

Sarepta's interpretation also improperly renders the claim language "comprising a base sequence" superfluous. *Wasica Fin. GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1288 n.10 (Fed. Cir. 2017) ("It is highly disfavored to construe terms in a way that renders them void, meaningless, or superfluous."); *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950-51 (Fed. Cir. 2006) (rejecting construction that would render another limitation superfluous). As Dr. Hastings explains:

> If it is true, as Dr. Stein asserts, that only "the entire linear sequence of bases in an antisense oligonucleotide forms a base sequence, *i.e.*, the overall length of an antisense oligonucleotide is the same as the length of the base sequence itself," Ex. 37 ¶51, then the claim means exactly the same as if the language "comprising a base sequence" were deleted:
>
> > An antisense oligonucleotide of 20 to 31 bases ~~comprising a base sequence~~ that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA…

Ex. 43 ¶35. As such, the patentee's choice to recite "base sequence" as a separate claim term from "antisense oligonucleotide" would "confirm[] to a POSA that the 'base sequence' may be a subsidiary portion of the 'antisense oligonucleotide,' and does not exclusively mean the entire length of the 'antisense oligonucleotide.'" *See id.* ¶36.

Similarly, surrounding claim language demonstrates that Sarepta's view of the "100% complementary" limitation is incorrect. According to Sarepta, the entire "antisense oligonucleotide" must be 100% complementary to the "target region." *See, e.g.*, Br. 8 ("[T]he bases of the antisense oligonucleotide collectively form a sequence ('base sequence') that is 100% complementary to a segment of the pre-mRNA ('target region')…."). But the claims recite differently. "[T]hey require (1) that the 'antisense oligonucleotide of 20 to 31 bases compris[es] a base sequence'; and (2) that a portion of the antisense oligonucleotide—the '**base sequence**'—is 100% complementary," and (3) that "complementarity [be] to '**consecutive bases of** a target region," rather than the 'target region' as a whole." Ex. 43 ¶¶34-36.



Thus, Sarepta's interpretation "materially changes how the '100% complementary' limitation operates." *Id.* ¶86.

(b) The Remaining Intrinsic Evidence Supports NS's Construction

The specification discloses multiple antisense oligonucleotide embodiments that, contrary to Sarepta's view, include more than a single sequence of bases that is 100% complementary to one consecutive segment of pre-mRNA, as Sarepta's proposed construction requires.

First, the specification discloses "weasel" embodiments of antisense oligonucleotides. *See, e.g.*, '851 Patent 4:56-62 (identifying a prior art example), 23:43-57 (noting that "'weasels' [are] preferably selected from…Table 1C."). As the specification explains, a "weasel" is a "cunningly designed antisense oligonucleotide" formed "by joining together two or more antisense oligonucleotide molecules." '851 Patent 4:56-62. As a result, weasels are antisense oligonucleotides that "include sequences of bases that are each complementary to a different region of pre-mRNA." Ex. 43 ¶40. Excluding these expressly disclosed embodiments of multiple base sequences within a broader oligonucleotide would be legally incorrect. *SynQor, Inc. v. Artesyn Techs., Inc.*, 709 F.3d 1365, 1378-79 (Fed. Cir. 2013) ("A claim construction that 'excludes the preferred embodiment is rarely, if ever, correct and would require highly persuasive evidentiary support.") (quoting *Adams Respiratory Therapeutics, Inc. v. Perrigo Co.*, 616 F.3d 1283, 1290 (Fed. Cir. 2010)).

Second, the shared specification also explains that the overall "sequence of an antisense molecule **need not be 100% complementary** to that of its target sequence to be specifically hybridisable." '851 Patent 25:26-28. "[A] sufficient degree of complementarity or precise pairing such that stable and specific binding occurs between the oligonucleotide and the DNA or RNA target" is enough to make an antisense oligonucleotide "specifically hybridisable." *Id.* at 25:22-35. As Dr. Hastings explains, this comports with her understanding of the "base sequence" limitations, which "define a core set of bases within the 'antisense oligonucleotide' that would ostensibly provide a 'sufficient degree of complementarity or precise pairing' to make the antisense oligonucleotide 'specifically hybridisable.'" Ex. 43 ¶39.

Sarepta ignores these embodiments and instead urges the Court construe based on the particular embodiments found in Table 1A listing "nucleotide sequence[s]" for entirely complementary antisense oligonucleotides. *See* Br. 17; Ex. 37 ¶69. In doing so, Sarepta asks to Court to "commit[] one of the cardinal sins of patent law—reading a limitation from the written description into the claims." *SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340 (Fed. Cir. 2001); *KCJ Corp.*, 223 F.3d at 1356 ("[P]articular embodiments appearing in a specification will not be read into the claims when the claim language is broader than such embodiments.").

Sarepta's reliance on Table 1A fails to consider how a POSA would understand that disclosure in the context of the entire specification. Certain "nucleotide sequence[s]" listed Table 1A are likewise listed in Table 1C. *Compare* '851 Patent, col. 19 (listing SEQ ID NO: 194, 195, and 196 for exon 53), *with* col. 21 (listing same). But when listed in Table 1C, these same "nucleotide sequence[s]" only constitute **part** of the weasel-style antisense oligonucleotides.

"Taking the specification as a whole thus demonstrates that the claim term 'base sequence' encompasses both constituent base sequences **and** entire base sequences." Ex. 43 ¶43.

Sarepta's construction also ignores passages from the prosecution history showing that the Patent Office interpreted the claims as NS proposes. *See Phillips*, 415 F3d at 1317 ("[T]he prosecution history provides evidence of how the PTO and the inventor understood the patent."). When responding to an obviousness rejection for the '851 Patent, Applicant acknowledged the Office's reliance on "SEQ ID NO: 29 (h53AON1), which [the Office] contends is a 18-mer oligonucleotide **having a sequence identical to three nucleotides** of SEQ ID NO: 195." Ex. 22, at SRPT-VYDS-0004785. As Dr. Hastings explains, "[t]his statement uses the same meaning for 'sequence' that NS proposes for Term 1a." Ex. 43 ¶46 ("[T]he prior art antisense oligonucleotide spanning 18 bases includes a constituent 'sequence' spanning only 3 bases…."). This understanding is reflected in the Office's argument that "the skilled artisan would 'try' to enhance activity by 'a common and efficient strategy' of synthesizing and testing 'longer oligonucleotides **containing within them the sequence** known to have the desired activity.'" Ex. 22, at SRPT-VYDS-0004789; Ex. 43 ¶47.

Federal Circuit law and the intrinsic evidence squarely support NS's proposed construction. The Court should therefore construe "a base sequence" as "any sequence of bases that is part of the antisense oligonucleotide."

ii. Term 1b – "a target region"

"A patent is indefinite 'if its claims, read in light of the specification … and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.'" *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1340-41 (Fed. Cir. 2015) (quoting *Nautilus*, 572 U.S. at 901). To avoid indefiniteness, "a patent must be precise enough to afford clear notice of what is claimed, thereby appris[ing] the public of what is still open to them."

Id. at 1341. In other words, "[a] claim may be indefinite if the patent does not convey with reasonable certainty how to choose among multiple possible constructions for a particular limitation." *Vaxcel Int'l Co. v. Heathco LLC*, No. 20-224-LPS, 2021 U.S. Dist. LEXIS 224684, at *6 (D. Del. Nov. 22, 2021) (citing *Teva*, 789 F.3d at 1341). The "'classic' situation" of indefiniteness arises when "competing claim constructions may produce conflicting infringement findings, yet a POSA has no way to choose between the proposed constructions." *Id.* at *14.

Such is the case with "a target region." Term 1b is recited in each independent claim of the UWA Patents and found immediately after the language "consecutive bases of." *See, e.g.*, '851 Patent, cl. 1. As shown below, the full phrase in which the term appears is "a target region of exon 53 of the human dystrophin pre-mRNA":

> 1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69), wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

Id. This surrounding context suggests only that the recited "target region" is "some portion of some human, exon 53 pre-mRNA."[7] *See* Ex. 43 ¶53.

With this limited guidance, however, "a POSA would not be reasonably certain regarding what portion(s) of the pre-mRNA must be 'targeted' to satisfy this claim language." *Id.* As Dr.

[7] In the '851 Patent, a subsequent "wherein" clause ("wherein the target region is within…") purports to provide some additional description on the location of the "target region." *See* '851 Patent, cl. 1. But this language itself gives rise to indefiniteness. *See infra* Term 2. Moreover, Sarepta's proposed construction for Term 2 does not resolve the definiteness issue here.

Hastings explains, "POSAs at the time of the invention (and still to this day) did not consistently use 'target' to refer to any specific sequence of pre-mRNA." *Id.* ¶54. The UWA Patents' "shared specification actually illustrates this, as it refers to 'targeting' a portion of pre-mRNA in at least three separate ways." *Id.*

First, the specification repeatedly uses "target" to identify less than the entire pre-mRNA of the exon of interest—namely, "to refer to the particular motifs or regulatory regions on a pre-mRNA transcript being targeted (*e.g.*, acceptor site, donor site, enhancers, silencers)." Ex. 43 ¶¶54-57 (describing exemplary disclosures). These regulatory elements are "often important sequences for modulating splicing activity, as they represent locations where the proteins involved in splicing interact with the pre-mRNA transcript." *Id.* ¶57. The specification expressly identifies regulatory regions as "preferred target site(s)" and "[t]he most obvious or readily defined targets for splicing intervention." '851 Patent 25:12-17, 4:30-38, 3:22-29 (discussing research into "oligonucleotides **targeted** to splice sites"), 3:67-4:3 (discussing prior work by co-inventor Wilton "**targeting** the acceptor region of the mouse dystrophin pre-mRNA"), 23:24-28 (describing "antisense molecule(s)…**targeted** to nucleotide sequences involved in splicing").

Second, the specification also uses "target" to refer more narrowly to "the exact bases of pre-mRNA to which an antisense oligonucleotide anneals (or binds)." Ex. 43 ¶¶54, 58 (describing exemplary disclosures). For example, the specification discusses "[a]nnealing sites…selected for examination" where the "2OMe antisense oligonucleotides were designed to be complementary to **the target sequences**." '851 Patent 32:31-36. In other locations, the specification describes "**binding** to specified dystrophin pre-mRNA **targets**" and "**binding** to a selected **target.**" *Id.* at 23:38-45, 4:44-46 (referring to "binding to a selected **target**").

And *third*, the specification repeatedly uses "target" to broadly identify an exon of interest. *See* '851 Patent 23:62-24:3 (referencing "some **targets** such as exon 19," and "some other **targets**, such as murine dystrophin exon 23"), 24:21-25 (noting that "[i]n other exons **targeted** for removal, masking the donor splice site did not induce any exon skipping"), 23:31-35; Ex. 43 ¶56 (describing exemplary disclosures).

Sarepta and Dr. Stein unilaterally adopt the second, annealing site meaning without reconciling it with the specification's conflicting usage. *See* Br. 11 ("A skilled artisan also would have understood that 'a target region' refers to a segment of the pre-mRNA that the claimed antisense oligonucleotide is complementary to.") (citing Ex. 37 ¶¶63-64). Indeed, as Dr. Hastings observes, they "fail[] to recognize that the specification **only** uses the exact language 'target region' twice, and that neither of those usages apply the annealing site meaning." Ex. 43 ¶63. Rather, both plainly refer to regulatory pre-mRNA regions as the "target." *Id.*; '851 Patent 4:30-38, 22:44-53. "Thus, from the available options…a POSA would not find it reasonably certain that the claim language 'target region' has the annealing site meaning." Ex. 43 ¶63.

Importantly, applying these different meanings to the "target region" limitation produces materially different claim scopes. "[I]f 'target region' refers to the regulatory elements involved with splicing, then Term 1b imposes a requirement that the 'consecutive bases' on the pre-mRNA to which the 'base sequence' is '100% complementary' be from such an element." *Id.* ¶60. But if "'target region' refers to the segment of pre-mRNA of exon 53 to which a given antisense oligomer happens to anneal, then Term 1b would impose a requirement tailored to the specific antisense oligonucleotide binding site." *Id.* ¶61 (internal citation omitted).

The claims' recitation of "a target region" therefore leaves a POSA without reasonable certainty regarding their scope. Sarepta's proposed construction fails to resolve this uncertainty—

it merely identifies a "target region" as some pre-mRNA "segment." That fails to reflect the "annealing site" meaning that Dr. Stein adopts and does not clarify which usage of "target region" the claims employ. As such, the UWA Patents are invalid as indefinite. *Id.* ¶67.

iii. Term 1c – "exon 53 of the human dystrophin pre-mRNA"

The phrase "exon 53 of the human dystrophin pre-mRNA" also renders the claims indefinite because it is unclear whether this limitation refers to normal or mutated pre-mRNA. Using the '827 Patent, claim 1 as an example, Term 1c immediately follows Term 1b ("a target region"):

> **1**. A method for treating a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation of the DMD gene that is amenable to exon 53 skipping, comprising administering to the patient an antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

Ex. 3, '827 Patent, cl. 1.

Although "the dystrophin gene was identified in the 1980s, and subsequent research has identified the typical nucleotide sequences associated with its various exons, including exon 53," (Ex. 43 ¶70; Ex. 37 ¶34), this consensus sequence reflects the normal dystrophin gene, "commonly called the 'wildtype' gene." Ex. 43 ¶70. But "DMD patients do not have a wildtype dystrophin gene," they "instead have 'mutations in the[ir] dystrophin gene.'" *Id.* ¶71 (quoting Ex. 37 ¶35;

'851 Patent 24:64-25:2 (explaining that DMD "arises from mutations that preclude the synthesis of a functional dystrophin gene product").

Importantly, a variety of different mutations can lead to DMD. As the specification explains, "Duchenne muscular dystrophy gene defects are typically nonsense mutations or genomic rearrangements such as deletions, duplications or microdeletions or insertions that disrupt the reading frame," and "there are many positions where these mutations can occur." '851 Patent 24:64-25:6. And, according to the UWA Patents, the underlying logic of antisense technology is to disrupt normal splicing by annealing antisense oligonucleotides to "exons associated with disease-causing mutations." *Id.* at 2:42-54. This concept is illustrated by Figure 2, in which the "hatched box represents an exon carrying a mutation" and the "solid black bar represents an antisense oligonucleotide that prevents inclusion of that exon":

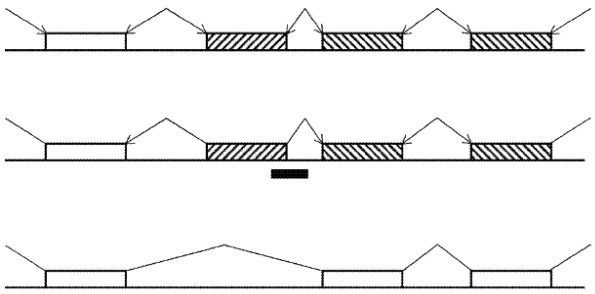


FIGURE 2

Id. at Fig. 2, 5:35-40.

"With this background in mind," Dr. Hastings explains, "a POSA would immediately find it unclear whether the claim term 'exon 53 of the human dystrophin pre-mRNA' refers to exon 53 from wildtype pre-mRNA or patient's mutated pre-mRNA." Ex. 43 ¶73. This "leaves a POSA with two possible interpretations for the meaning of 'exon 53 of the human dystrophin pre-mRNA,' each with a different resulting claim scope." *Id.* ¶79. "If Term 1c refers to the wildtype

pre-mRNA, then the 'complementary' limitation of the asserted claims will be evaluated against the wildtype pre-mRNA sequence." *Id.* "But if it refers to a patient's mutated pre-mRNA, that limitation will be evaluated against the mutated pre-mRNA sequence for exon 53, which may…differ from the wildtype sequence, depending on the patient." *Id.*

The intrinsic evidence does not resolve this uncertainty. The '851 and '590 Patents' claims "do not provide any antecedent basis for 'the human dystrophin pre-mRNA'—Term 1c is the first (and only) time those claims recite pre-mRNA." *Id.* ¶74. And while the '827 Patent's independent claim 1 does not provide express antecedent basis either, its preamble recites "a patient with Duchenne muscular dystrophy (DMD) in need thereof who has a mutation of the DMD gene that is amenable to exon 53 skipping." '827 Patent, cl. 1. While not dispositive, this additional language "suggest[s] a mutated pre-mRNA" to a POSA. *See* Ex. 43 ¶75.

Looking to the "shared specification does not resolve the uncertainty either, as it describes experiments conducted with both wildtype and mutated cell lines." *Id.* ¶76. The Background Section, for example, describes a study analyzing the ability of "a 31-mer 2'-0-methyl oligoribonucleotide" to "inhibit[] splicing of **wild-type pre-mRNA**," '851 Patent 3:8-21, alongside another study testing "in the **mdx mouse mutant**, a model for muscular dystrophy" in which "[a]n antisense oligonucleotide targeted to the 3' splice site of murine dystrophin intron 22 was reported to cause skipping of the **mutant** exon." *Id.* at 3:22-40. Disclosures relating to the UWA inventors' own work likewise describe both types of pre-mRNA. The specification "describes a series of experiments conducted by the inventors using normal human tissue, *i.e.*, the wildtype pre-mRNA." Ex. 43 ¶77 (quoting the '851 Patent's passage at column 32, lines 48-55 regarding "**normal primary myoblast cultures**"). But it also explains that "the invention provides a method for treating **a patient** suffering from a genetic disease **wherein there is a**

mutation in a gene encoding a particular protein and the effect of **the mutation** can be abrogated by exon skipping." '851 Patent 5:1-7.

Thus, neither the claims nor other intrinsic evidence "inform those skilled in the art about the scope of the claimed inventions with reasonable certainty due to each of their recitation of 'exon 53 of the human dystrophin pre-mRNA.'" Ex. 43 ¶80. As such, the Court should find the UWA Patents invalid as indefinite.

c. Sarepta's Reply Position

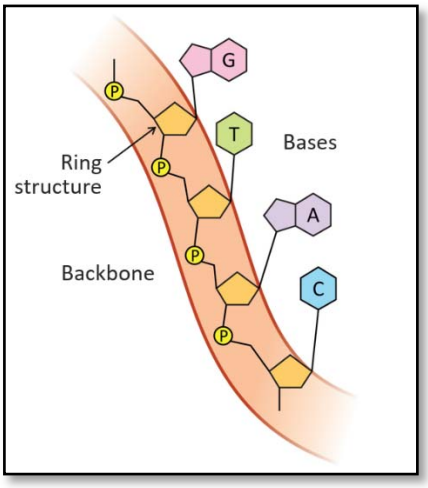
i. Term 1a - "a base sequence"

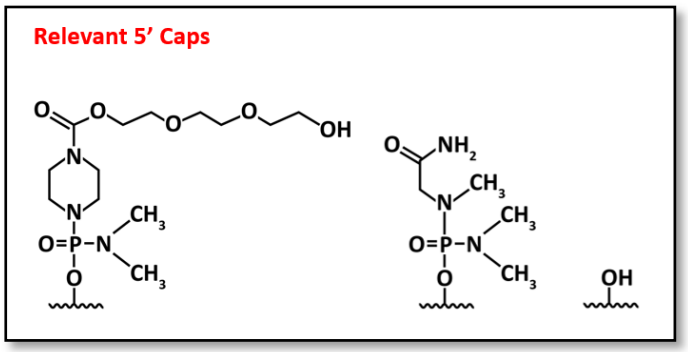
(a) When Read in Context, Sarepta's Construction Conveys the Term's Plain Meaning

Sarepta proposes construing "a base sequence" as "a linear sequence of bases." Each asserted claim recites an "*antisense oligonucleotide* of 20 to 31 bases *comprising a base sequence* that is 100% complementary to consecutive bases of a target region of exon 53." In other words, the "base sequence" *of the antisense oligonucleotide* must be "20 to 31 bases" in length and "100% complementary" to a target region of exon 53. Stein Decl. ¶¶50-52. A skilled artisan would understand that the "base sequence" includes *all* of the bases in the antisense oligonucleotide. Had the patentee intended otherwise, it would have specified that the antisense oligonucleotide had multiple, distinct base sequences. Stein Rep. Decl. ¶¶7, 15.

NS nevertheless argues that the term "comprising" in the claims permits multiple "base sequences" to be present in each antisense oligonucleotide. Br. 18-19. Not so. Stein Rep. Decl. ¶¶8-9. As NS acknowledges, the claim term "comprising" means "that [i] the named elements are essential, but [ii] other elements may be added and still form a construct within the scope of the claim." Br. 19 (quoting *Genentech*, 112 F.3d at 501). Sarepta's construction (i) requires the "base sequence" of the antisense oligonucleotide to be "100% complementary" to the target region, as

this is an essential claim element. And (ii) it allows for other elements to be present in the antisense oligonucleotide, such as a chemical backbone and 5' cap, illustrated below:





NS also argues that Sarepta's construction renders the term "comprising a base sequence" superfluous. *Id*. at 20. But Sarepta's construction clarifies that the antisense oligonucleotide's bases as linearly arranged must be 100% complementary to the target region, thereby excluding oligonucleotides having the same bases arranged in a different order. Stein Rep. Decl. ¶¶10-12.

In contrast, NS's construction eviscerates an essential element of the claims—"a base sequence that is 100% complementary." Using "comprising" as a pretext, NS wrongly eliminates the requirement for 100% complementarity by expanding the claims to cover multiple "base sequences," including non-complementary base sequences. Br. 17-21; Stein Rep. Decl. ¶¶12-16. But a claim's use of "comprising" does not allow a court to "abrogate claim limitations." *Wis. Alumni Rsch. Found. v. Apple Inc.*, 905 F.3d 1341, 1348 n.8 (Fed. Cir. 2018). The Court should reject NS's attempt to eliminate the requirement for 100% complementarity.

(b) The Specification and Prosecution History Support Sarepta's Construction

The specification and prosecution history support Sarepta's construction. In describing each exemplary antisense oligonucleotide, the specification identifies the corresponding

"sequence" as the string of linearly arranged bases in the oligonucleotide. Ex. 1 at cols. 7-19 (Table 1A). It also equates an antisense oligonucleotide's length with the number of bases found in its "sequence." *Id.* at 23:63-24:3, 25:61-26:3. And the Patent Office used the term "nucleobase sequence" to indicate that *all* bases in the claimed antisense oligonucleotide are complementary to the target region. *See* Ex. 17 at 3.

NS presents three unpersuasive responses. First, NS argues that so-called "weasel" embodiments in the specification support its construction. Br. 21. But as the specification explains, a weasel is formed by "joining together *two or more* antisense oligonucleotides," whereas the claims are directed to "an" oligonucleotide. *Compare* Ex. 1 at 4:56-62, *with id.* at claim 1. Consistent with this point, the sole, exemplary exon 53 weasel contains *three* antisense oligonucleotides, is *over 75* nucleotides long, includes *non-complementary* nucleotides, and targets both exons and *introns*. *Id.* at Table 1C; Stein Rep. Decl. ¶20. In contrast, the claims require "an" antisense oligonucleotide that is 20-31 bases long and 100% complementary to *exon* 53. Ex. 1 at claim 1. The claims are not directed to weasels, and these embodiments are irrelevant to their construction. *See Nazomi Commc'ns, Inc. v. Arm Holdings, P.L.C.*, 403 F.3d 1364, 1369 (Fed. Cir. 2005) (claims can embrace subject matter that differs from embodiments illustrated in the specification).

Second, NS notes that the specification discusses antisense molecules that are not 100% complementary to their target sequences. *See* Br. 22 (quoting '851 Patent 25:26-28). But the claims expressly require *100% complementarity*. Ex. 1 at claim 1. That the specification also contemplates oligonucleotides having less than 100% complementarity cannot eliminate this limitation. Stein Rep. Decl. ¶¶17-19. Moreover, NS's construction is inconsistent with the specification's teachings. Under NS's construction, a claimed antisense oligonucleotide can

include a majority of non-complementary bases. *Id.* The specification cautions against using such oligonucleotides "to avoid non-specific binding" to "non-target sequences." Ex. 1 at 25:28-38.

Third, NS argues that an out-of-context statement from the prosecution history supports its construction. Br. 23. Not so. Stein Rep. Decl. ¶¶21-22. In distinguishing a prior art oligonucleotide (h53AON1) that was 18 bases long, the applicant explained that it had "a sequence identical to three nucleotides of SEQ ID NO: 195." Ex. 22 at SRPT-VYDS-0004785. The applicant's diagram and accompanying statement, reproduced below, clarify that h53AON1 contained a single base sequence having "three consecutive bases of SEQ ID NO: 195," not, as NS alleges, two or more base sequences. *Id.* at SRTV-VYDS-0004786.

1. CUGAAGGUGUUCUUGUACUUCAUCC SEQ ID NO: 195
2. CUGUUGCCUCCGGUUCUG h53AON1
3. CUGUUGCCUCCGGUUCUGAA h53AON1+**2** bases = 20mer
4. CUGUUGCCUCCGGUUCUGAAGGUGUUC h53AON1+**9** bases = 27mer

As can be seen from above and acknowledged by the Office, h53AON1 comprises only three consecutive bases of SEQ ID NO: 195 indicated in the underlined portion of lines 1 and 2.

In sum, Sarepta's construction is consistent with the intrinsic and extrinsic evidence, conveying that the antisense oligonucleotide's bases form a linear sequence of bases that are 100% complementary to a target region of exon 53. NS's overly broad construction should be rejected.

ii. Term 1b - "a target region"

(a) Sarepta's Construction Is Consistent with the Intrinsic and Extrinsic Evidence

Sarepta proposes construing "target region" as a "segment of the pre-mRNA." This construction conveys that the "target region" refers to the pre-mRNA segment to which the claimed antisense oligonucleotide is intended to bind. Stein Decl. ¶¶63-64; Stein Rep. Decl. ¶23. As NS's expert Dr. Hastings acknowledges, the specification "*repeatedly* uses 'target' to refer to the particular annealing sites of antisense oligonucleotides." Hastings Decl. ¶58.

Sarepta's construction conforms to how the term is understood in the art, as contemporaneous articles illustrate. Stein Decl. ¶¶53-57; Stein Rep. Decl. ¶24. Indeed, Dr. Hastings has repeatedly used the same term in the same manner in her own publications. Ex. 48 at 250 (antisense oligonucleotides "are short oligonucleotides, typically 15–25 bases in length, which are the reverse complement sequence of a specific RNA transcript *target region*"); Ex. 49 at 6550 ("[A]ll [antisense oligonucleotides] make use of short nucleic acids that specifically base-pair to a *targeted sequence*."). NS nowhere disputes that it previously adopted the same meaning for "target region" during prosecution of one of its asserted patents.

(b) NS's Indefiniteness Theory Is Flawed

While NS acknowledges that Sarepta's construction is supported by the specification (Br. 26 ("Sarepta and Dr. Stein unilaterally adopt the second, annealing site meaning")), it nevertheless contends that the claims are indefinite because the specification uses the term "target" in two other contexts, purportedly resulting in "different claim scopes." *Id.*

NS applies the wrong legal standard. A claim satisfies the definiteness requirement if, in light of the specification and prosecution history, it informs a skilled artisan about the scope of the invention with reasonable certainty. *Nevro Corp. v. Bos. Sci. Corp.*, 955 F.3d 35, 41 (Fed. Cir. 2020). Indefiniteness is *not* established by showing that a claim is "susceptible to different interpretations" because "[s]uch a test would render nearly every claim term indefinite so long as a party could manufacture a plausible construction." *Id.*; Br. 25-27. Nor is indefiniteness established where different interpretations could result in different claim scopes. *Nautilus*, 572 U.S. at 908-09 (rejecting a test rendering a claim invalid where "readers could reasonably interpret the claim's scope differently"). Here, the claims are not indefinite because a skilled artisan would have understood the term "target region" with reasonable certainty.

Indeed, NS's alternative constructions make no sense when the term "target region" is evaluated in the context of the claims. Stein Rep. Decl. ¶¶25-29. NS argues that the specification sometimes uses the *word* "target" to refer to "particular motifs or regulatory regions on a pre-mRNA transcript being targeted." Br. 25. But nothing in the claims suggests that the *term* "target region" refers to these motifs (e.g., exonic splicing enhancer elements). Instead, the claims define the target region positionally as a segment of exon 53, for example by requiring at least 12 consecutive bases of SEQ ID NO: 195 (nucleotides +23+47 of exon 53) and 100% complementarity.

NS also argues that the *word* "target" is sometimes used in the specification to "broadly identify an exon of interest." *Id.* at 26. But nothing in the claims suggests that the *term* "target region" broadly refers to the whole exon. The claims already identify exon 53 as the exon of interest. Read in context, the target region refers to the segment of exon 53 pre-mRNA to which the claimed antisense oligonucleotide is intended to bind. Because a skilled artisan would have no difficulty understanding this term, it is not indefinite. *Vaxcel*, 2021 WL 7209508, at *5.

NS offers no evidence that it matters which of its interpretations is adopted. *See Bristol-Meyers Squibb Co. v. Mylan Pharms. Inc.*, C.A. No. 09-651-LPS, 2013 WL 12322088, at *13 (D. Del. Oct. 17, 2013) (holding that "hypothetical speculation" did not constitute clear and convincing evidence of indefiniteness when no evidence showed how competing constructions were pertinent). Here, NS's Viltepso® infringes the claims under any construction because it is 100% complementary to exon 53; a segment in the pre-mRNA on exon 53; and a segment including splicing factor binding sites. Stein Rep. Decl. ¶¶30-34; *see also* Ex. 50 at S352. NS offers no evidence that "competing claim constructions may produce conflicting infringement findings." Br. 24.

Because a skilled artisan would have understood with reasonable certainty that "target region" refers to a segment in the pre-mRNA, NS's flawed indefiniteness theory should be rejected.

iii. Term 1c - "exon 53 of the human dystrophin pre-mRNA"

Sarepta proposes construing the term "exon 53 of the human dystrophin pre-mRNA" as "the pre-mRNA transcribed from exon 53 of the human dystrophin gene." NS asserts that the term is indefinite because it is allegedly unclear whether this limitation refers to wild-type (normal) or mutated pre-mRNA. Br. 27-30.

A skilled artisan would have understood this term to refer to the wild-type sequence of exon 53 of the human dystrophin pre-mRNA. Stein Rep. Decl. ¶¶35-36. This sequence was well known in the art, as Drs. Stein and Hastings acknowledge. Hastings Decl. ¶70; Stein Decl. ¶65. Consistent with the state of the art, the claims refer to exon 53 of "the" human dystrophin pre-mRNA, i.e., "the" sequence known in the art. Br. 11-12; Stein Decl. ¶65. The prosecution history of the '851 patent confirms this understanding. *See* Ex. 22 at SRPT-VYDS-0004609-10 (Examiner explaining that the antisense oligonucleotide's base sequence is determined by comparison to the exon 53 sequence "identified" in the prior art).

NS's purported confusion is unpersuasive. NS notes that the specification discusses experiments conducted with "mutated cell lines." Br. 29-30. But NS fails to explain how these experiments—studying a *different* exon in a *non-human* cell line—inform the meaning of the term "exon 53 of *the human* dystrophin pre-mRNA." Stein Rep. Decl. ¶¶37-40.

NS also speculates that there *may* be DMD patients with mutated forms of exon 53 pre-mRNA, and notes that one asserted patent is directed to treating DMD. Br. 27-29. The existence of such patients would not impact the plain meaning of this art-recognized term. Stein Rep. Decl. ¶¶41-42. Moreover, NS offers no evidence that exon 53 is mutated in *any* DMD patients amenable

to treatment by exon 53 skipping. Br. 27-30. The Court should "not appease [NS] and find indefiniteness based on a hypothetical possibility." *Purdue Pharm. Prods. L.P. v. Actavis Elizabeth L.L.C.*, C.A. No. 12-5311, 2015 WL 5032650, at *57 (D.N.J. Mar. 27, 2015). Further, the term should be construed "consistently across all asserted patents," including the other asserted Wilton patents that use the *same claim term without referencing DMD patients*. *See* Exs. 1 & 2 at claim 1; *SightSound Techs., L.L.C. v. Apple Inc.*, 809 F.3d 1307, 1316 (Fed. Cir. 2015). Consistent with its common usage in the field, this term refers to the wild-type (normal) human pre-mRNA.

d. Nippon's Sur-Reply Position

i. Term 1a – "a base sequence"

Sarepta cannot dispute that, under Federal Circuit law, "A" comprising "B" means that "A" includes, but is not limited to, "B." Br. 30. Here, "A" is the "antisense oligonucleotide," and "B" is a portion of that "antisense oligonucleotide"—namely, "a base sequence"—that "is 100% complementary to consecutive bases in a target region." The claims' structure makes clear that (1) the recited "base sequence" is an "essential" part of the claimed "antisense oligonucleotide" and (2) "other elements may be added and still form a construct within the scope of the claim." *Genentech*, 112 F.3d at 501.

Federal Circuit law does not limit what these "other elements" may be. *Id.* And, when a term, like "base sequence," is preceded by the indefinite article "a" it indicates plurality, *i.e.*, "that the claimed invention is not limited to only one" of that term. *Persawvere, Inc. v. Milwaukee Elec. Tool Corp.*, No. 21-cv-400-GBW, 2023 WL 2140033, at *5 (D. Del. Feb. 21, 2023) (holding that "a hand grip portion" permitted the claimed apparatus to have more than one "hand grip portion"). Sarepta's construction improperly excludes "other elements," such as additional bases and base sequences, and cannot be correct. That Sarepta's construction allows for some, non-excluded elements cannot correct this defect. The non-exclusive meaning of "comprising" carries a non-

exclusive meaning generally, *Genentech*, 112 F.3d at 501, and Sarepta may not arbitrarily deem particular types of "other elements" excluded.

Moreover, Sarepta's construction is inconsistent with the scope of embodiments in the specification. In support, Sarepta cites to Table 1A's listing of "nucleobase sequence[s]" in which the sequences are "100% complementary" and commensurate in length with the described oligonucleotide. Br. 32. However, Sarepta does not dispute that the specification further discloses "antisense molecules that are not 100% complementary." Br. 32. And, Sarepta's attempts to distinguish "weasels" by arguing that a "weasel" includes multiple oligonucleotides is unavailing. Br. 32. The specification describes the disclosed "weasel" as being a "cunningly designed **antisense oligonucleotide**" in the singular, '851 Patent 4:56-62, which is consistent with a POSA's understanding. Ex. 43 ¶¶40-41. Thus, the specification supports NS's proposed construction, which gives proper breath to the "comprising" language.

Sarepta's construction also runs afoul of several basic canons of claim construction. *See* Br. 20-21. Sarepta's construction renders "base sequence" superfluous by improperly conflating it with "antisense oligonucleotide." *See Wasica*, 853 F.3d at 1288 n.10. Indeed, Sarepta assumes, without support, that "a base sequence" must have all bases in the "antisense oligonucleotide." *See* Br. 30-31. Sarepta then improperly applies the claim's requirements for "a base sequence"—that it is "100% complementary to consecutive bases in a target region"—to the entire "antisense oligonucleotide." *See id.* at 30. But, that is not what the claim says. As written, the claim requires only that some "consecutive bases" of "a base sequence" are "100% complementary to a target region," not the "antisense oligonucleotide" as a whole. *See Bd. of Regents of the Univ. of Texas Sys. v. BENQ Am. Corp.*, 533 F.3d 1362, 1371 (Fed. Cir. 2008) ("Different claim terms are

presumed to have different meanings."). Sarepta's construction improperly rewrites the claim, materially changing claim scope, and should be rejected.

Sarepta, also incorrectly asserts that NS's construction "eviscerates an essential element of the claims—'a base sequence that is 100% complementary.'" Br. 31. Not so. NS's construction merely applies the "100% complementary" requirement to the intended claim element—"consecutive bases" within "a base sequence," and thus correctly reflects the claim's meaning.

Sarepta's remaining arguments are red herrings. First, Sarepta incorrectly suggests a dispute exists over "oligonucleotides having the same bases arranged in a different order," but ignores that NS's proposed construction also requires a "sequence of bases," not "bases" generally. Br. 31.[8] Second, Sarepta's discussion of the prosecution history misses the point. *Id.* at 36. Regardless of how one characterizes h53AON1, the applicant's statements use the term "sequence" when describing a subsidiary portion of h53AON1 "identical to three nucleotides of SEQ ID NO: 195." Ex. 22 at SRPT-VYDS-0004785. This use is consistent with NS's proposed construction—that a "sequence" or "base sequence" can be a subsidiary sequence of bases within the claimed "antisense oligonucleotide." The Court should construe Term 1a as NS proposes.

ii. Term 1b – "a target region"

Sarepta's reply mischaracterizes NS's arguments and the evidence and thus fails to address the issues with Term 1b that cause a POSA to lack reasonable certainty regarding claim scope. As NS's Response shows, NS applies the controlling *Nautilus* standard. NS does not merely argue that "target region" is "susceptible to different interpretations." Br. 35. Rather, NS asserts that "a POSA

[8] Sarepta ignores the fact that its "proposed construction for Term 1a individually…does not capture the concept" that the "base sequence" consists of all bases of the "antisense oligonucleotide," and no others. Br. 18 n.6.

has no way to choose between the proposed constructions," resulting in a "'classic' situation" of indefiniteness. *Vaxcel*, 2021 U.S. Dist. LEXIS 224684, at *14.

Sarepta's Reply also doubles-down on its assertion that the claimed "target region" is an annealing site and casts the alternatives as "mak[ing] no sense." Br. 35. But, it tellingly has no answer to the most cogent intrinsic evidence. As explained, "**the specification only uses the exact language 'target region' twice, and [] neither of those usages apply the annealing site meaning**"—they apply the regulatory element meaning.[9] Br. 26 (citing Ex. 43 ¶63; '851 Patent 4:30-38, 22:44-53). Thus, the regulatory element meaning is plainly one "competing construction" with the annealing site meaning as a second. Sarepta fails to identify any way a POSA could choose between (at least) these two meanings with reasonable certainty.

These different meanings are not immaterial, as they require fundamentally different inquiries to assess whether a given antisense oligonucleotide practices the "target region" limitation. Dr. Stein inadvertently illustrates this. Unlike the annealing site meaning, his analysis under the regulatory element meaning involves (1) assessing which pre-mRNA regions have regulatory elements[10] and (2) assessing whether the oligonucleotide at issue binds to those regions. Stein Rep. Decl. ¶33. Neither Sarepta nor Dr. Stein contest that "not every base of a given pre-mRNA

[9] Reliance on extrinsic evidence—whether Dr. Stein's testimony, publications, or unrelated NS patents—to overcome this intrinsic evidence would be legally erroneous. *Ruckus Wireless, Inc. v. Innovative Wireless Solutions, LLC*, 824 F.3d 999, 1003 (Fed. Cir. 2016) ("Legal error arises when a court relies on extrinsic evidence that contradicts the intrinsic record.").

[10] The extrinsic reference Dr. Stein relies upon to identify alleged regulatory regions of exon 53 does not disclose a consensus view, but describes certain predictive estimates obtained at that time from "three available algorithms." *Compare* Stein Rep. Decl. ¶ 33 (citing Fig. 1(a) and (b)), *with* Ex. 38 at 11:62-12:11 (describing same). Because resolution of Viltepso®'s alleged practice of the "target region" limitation goes to infringement and is inappropriate to consider at this stage, NS reserves argument. *Eon Corp. IP Holdings v. Silver Spring Networks*, 815 F.3d 1314, 1319 (Fed. Cir. 2016) (courts should not resolve "questions that…instead go to infringement" during claim construction).

transcript is associated with a regulatory motif," such that any given antisense oligonucleotide "may or may not" be complementary to such an element. Ex. 43 ¶60. This clear difference in how the infringement analysis proceeds under the competing constructions establishes indefiniteness—NS need not show confusion about a particular antisense oligonucleotide, much less Viltepso®. *Saso Golf, Inc. v. Nike, Inc.*, 843 F. App'x 291, 297 (Fed. Cir. 2021).

The Court should therefore hold the UWA Patents' claims indefinite.

iii. Term 1c – "exon 53 of the human dystrophin pre-mRNA"

Sarepta's analysis of Term 1c is similarly impermissible. Done properly, the claim construction inquiry begins with the "highly instructive" context provided by the claims, *Phillips*, 415 F.3d at 1314. Here, the '827 Patent recites "a patient with Duchenne muscular dystrophy (DMD…who has a mutation of the DMD gene." '827 Patent, cl. 1. The relevant inquiry is not whether a POSA would understand Term 1c in the abstract, but whether a POSA informed by this preceding recitation of a "patient…who has a mutation" would know with reasonable certainty whether the claims intended the wild-type or mutated sequence.

Sarepta cannot reconcile the conflict between its arguments (including Dr. Stein's opinions and the less-than clear prosecution history cited) and this language, so it asks the Court to ignore it. Br. 37 (requesting that the Court construe based on "other asserted Wilton patents that use the same claim term without referencing DMD patients"). This is backwards. The '827 Patent informs the meaning of these "other" two patents and demonstrates that the same uncertainty exists across all three. Moreover, the specification shared across all three patents also describes "the invention" to include "treating a patient" with "a mutation in a gene." '851 Patent at 5:1-7.

As such, the intrinsic evidence provides two competing options and leaves a POSA "no way to choose between the[m]," rendering the claims indefinite. *Vaxcel*, 2021 U.S. Dist. LEXIS 224684, at *14.

B. Term 3: "in which uracil bases are thymine bases"

Sarepta's Proposed Construction	NS's Proposed Construction
Not indefinite *No construction needed in light of inter alia, the intrinsic evidence and the knowledge of a person of ordinary skill in the art* To the extent construction is needed, Sarepta proposes that the phrase should be given its plain and ordinary meaning, i.e., "the antisense oligonucleotide has thymine bases instead of uracil bases"	*Indefinite*

1. Sarepta's Opening Position

a. A Skilled Artisan Would Have Understood that the Thymine Bases Phrase Modifies the Claimed Antisense Oligonucleotide

The intrinsic evidence establishes that thymine bases rather than uracil bases are used throughout the claimed antisense oligonucleotide, not in some unspecified portion of it. Because a skilled artisan would have understood the claim language, no construction should be necessary. But to the extent the Court construes this phrase, Sarepta's proposed construction conveys the plain and ordinary meaning. Stein Decl. ¶71.

The structure and syntax of the claim language show that the thymine bases phrase modifies the claimed antisense oligonucleotide. *See Credle v. Bond*, 25 F.3d 1566, 1572 (Fed. Cir. 1994) ("grammatical structure and syntax" may be instructive in interpreting a claim); Stein Decl. ¶¶72-73. For example, claim 1 of the '590 patent includes three "wherein" clauses and one "in which" clause (highlighted in orange), each set off by a comma (highlighted in blue):

> 1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA,
>
> wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195),
>
> in which uracil bases are thymine bases,
>
> wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and
>
> wherein the antisense oligonucleotide induces exon 53 skipping;
>
> or a pharmaceutically acceptable salt thereof.

The claim's syntax is clear: each clause, including the "in which uracil bases are thymine base" phrase, must be read as a separate limitation that modifies what is claimed as a whole—the "antisense oligonucleotide." *See Finisar Corp. v. DirecTV Grp., Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008) ("[W]hen a modifier is set off from a series of antecedents by a comma, the modifier should be read to apply to each of those antecedents."). If the thymine bases phrase were intended to refer to any other portion of the claim (e.g., the immediately preceding portion), there would have been no reason to use a comma to separate it from the rest of the claim. Reading the phrase in context, a skilled artisan would have understood it to modify the claimed antisense oligonucleotide as a whole.

The specification supports Sarepta's interpretation. *See Phillips*, 415 F.3d at 1313; Stein Decl. ¶¶74-75. In describing exemplary antisense oligonucleotides, the specification depicts uracil bases, not a mixture of uracil and thymine bases. Ex. 1 at Table 1A. The specification further explains that when these exemplified antisense oligonucleotides are constructed as a morpholino—as claimed here—the "U bases" (uracils) may be "T" bases (thymines), not some unspecified mixture of both. *Id.*

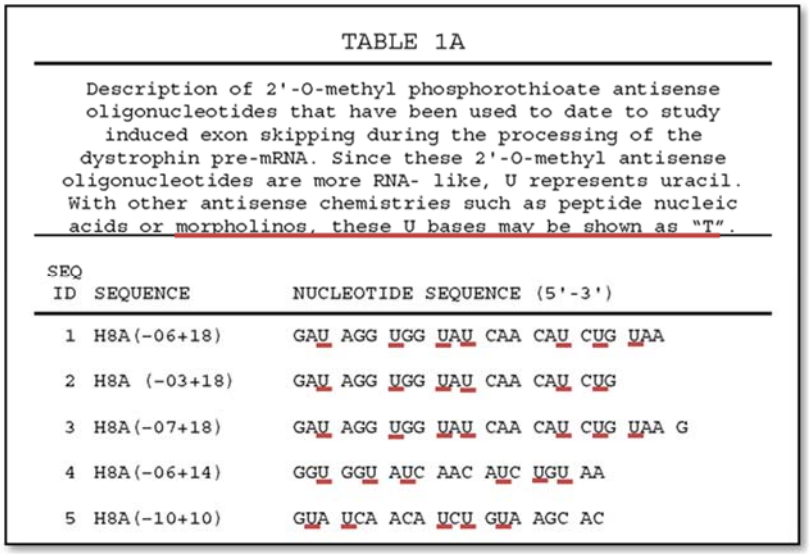


TABLE 1A

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to date to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
1	H8A(-06+18)	GAU AGG UGG UAU CAA CAU CUG UAA
2	H8A (-03+18)	GAU AGG UGG UAU CAA CAU CUG
3	H8A(-07+18)	GAU AGG UGG UAU CAA CAU CUG UAA G
4	H8A(-06+14)	GGU GGU AUC AAC AUC UGU AA
5	H8A(-10+10)	GUA UCA ACA UCU GUA AGC AC

Figure 2. Annotated Excerpt of Table 1A of the Wilton Patents (Stein Decl. ¶74)

The prosecution history of the '772 application—the parent of the Wilton patents—is consistent with this understanding. *See Capital Mach. Co. v. Miller Veneers, Inc.*, 524 F. App'x 644, 649 (Fed. Cir. 2013) ("[T]he prosecution history regarding a claim term is pertinent when interpreting the same term in both later-issued and earlier-issued patents in the same family."); Stein Decl. ¶¶76-79. The claims pursued in the '772 application were structurally identical to the Wilton patent claims:

Claim 1 of the '590 Patent	**Claim 1 of the '772 Application (Ex. 20 at SRPT-VYDS-0091345, -4178)**
1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA,	1. An antisense oligonucleotide of 25 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA,
wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195),	wherein the base sequence comprises at least 20 consecutive bases of C AUU CAA CUG UUG CCU CCG GUU CU GAAG GUG (SEQ ID NO: 193),
in which uracil bases are thymine bases,	in which uracil bases are thymine bases,
wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and	wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide,

Claim 1 of the '590 Patent	Claim 1 of the '772 Application (Ex. 20 at SRPT-VYDS-0091345, -4178)
wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.	wherein the antisense oligonucleotide induces exon 53 skipping, and wherein . . . .

In explaining the claimed subject matter of the '772 application, the applicant identified "uracil bases [being] thymine bases" as a feature of the claimed antisense oligonucleotide. Ex. 20 at SRPT-VYDS-0094179 ("*an **antisense oligonucleotide** having the following elements*: . . . (ii) 20 consecutive bases of SEQ ID NO: 193; *(iii) uracil bases are thymine bases*; (iv) the antisense oligonucleotide is a morpholino . . . ."). In responding to an obviousness rejection, the applicant similarly explained that "none of the cited references teach or suggest *combining the elements to result in the claimed **antisense oligonucleotide***," namely, "wherein the antisense oligonucleotide comprises 20 consecutive bases of SEQ ID NO: 193, **and** wherein uracil bases are thymine bases, **and** wherein the antisense oligonucleotide is a morpholino . . . ." *Id.* at SRPT-VYDS-0094181 (emphasis in original). These statements conform to how a skilled artisan would have read the same clause in the Wilton patents.[11]

As Dr. Stein explains, this reading of the thymine bases clause is consistent with how researchers typically design antisense oligonucleotides. Stein Decl. ¶¶80-83. Specifically, researchers generally use either uracil bases or thymine bases, but not both, in a single antisense oligonucleotide. *Id.* ¶80. This is to ensure synthesis feasibility and chemical and physical

[11] That the '772 application was later abandoned does not make the applicant's statements any less relevant. *Fenner Invs., Ltd. v. Cellco P'ship*, 778 F.3d 1320, 1325 (Fed. Cir. 2015) ("[T]he interested public has the right to rely on the inventor's statements made during prosecution, without attempting to decipher whether the examiner relied on them, or how much weight they were given."); *Microsoft Corp. v. Multi–Tech Sys., Inc.*, 357 F.3d 1340, 1350 (Fed. Cir. 2004) ("[A] patentee's statements during prosecution, whether relied on by the examiner or not, are relevant to claim interpretation.").

consistency of the synthesized antisense oligonucleotide. *Id.* Contemporaneous publications confirm this general practice of constructing antisense oligonucleotides with one type of base, either uracil or thymine, but not both. *Id.* ¶¶81-82.

Ex. 26

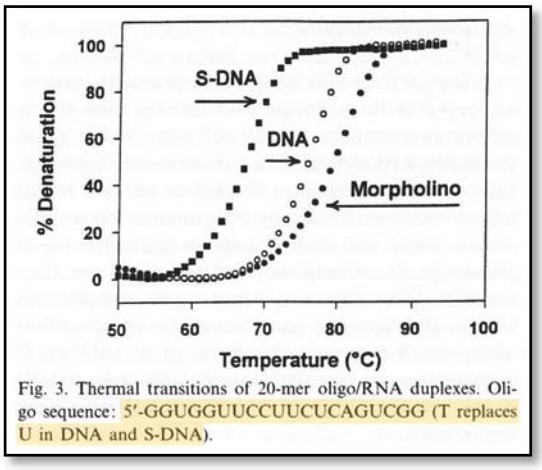


Fig. 3. Thermal transitions of 20-mer oligo/RNA duplexes. Oligo sequence: 5′-GGUGGUUCCUUCUCAGUCGG (T replaces U in DNA and S-DNA).

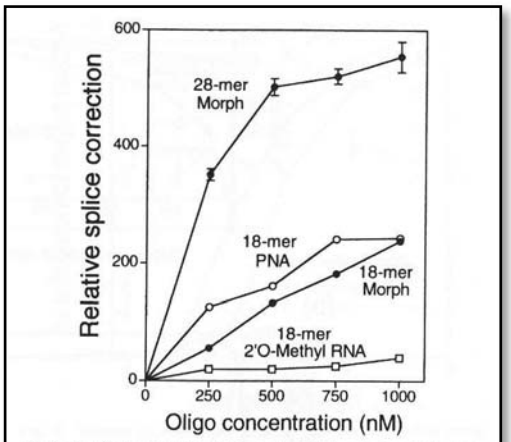


Fig. 6. Luciferase translated from corrected splicing of thalassemic globin/luciferase pre-mRNA in HeLa cells scrape-loaded with antisense oligos. Oligo sequences: 18-mer: 5′-CCTCTTACCTCAGTTACA; 28-mer: 5′-CCTCTTACCTCAGTTACAATTTATATGC.

Ex. 6

ID	Target	Indication	Phase of Development	Sequence 5'-3'
AVI-4126	*c-myc*	Restenosis	Phase 2 completed	ACGTTG AGG GGC ATC GTC GC
AVI-4126	*c-myc*	Polycyctic Kidney Disease	Phase 1b completed	
AVI-4126	*c-myc*	Solid Tumors	Phase 1 completed	
AVI-4126	*c-myc*	Pharmacokinetics	Phase 1 completed	
AVI-4557	CYP3A4	Drug Metabolism	Phase 1 Completed and in progess	CTG GGA TGA GAG CCA TCA CT
AVI-4020	West Nile	West Nile Viral	Phase 1b in progess	CTTAGACATCGAGATCTTCGT G

Figure 3. Sequences of Prior Art Antisense Oligonucleotides
(Stein Decl. ¶¶81-82)

b. The Thymine Bases Clause Is Not Indefinite

Guided by the claim language, specification, and prosecution history, a skilled artisan would have understood that the claimed antisense oligonucleotide includes thymine bases, not uracil bases. The thymine bases clause is therefore not indefinite. Ex. 36 at 26; *see supra*

§ IV.B.1.a; *Biosig*, 783 F.3d at 1376-77 (holding claims not indefinite in light of the claim language, prosecution history, and knowledge of a skilled artisan); *see 3M Co. v. Kerr Corp.*, No. 17-1730-LPS, 2019 WL 2411736, at *3 (D. Del. June 7, 2019) (considering "grammar and syntax" in determining definiteness); Stein Decl. ¶¶83-84.

2. Nippon's Responsive Position

The claim language, specification, and prosecution history provide a POSA with no way to determine the appropriate construction for the phrase "in which uracil bases are thymine bases," rendering the claims of the UWA Patents indefinite because it is not clear what portion of the claim this phrase modifies.

The indefiniteness of the claims of the UWA Patents arises from the fact that the antecedent basis for this limitation is not expressly stated. Instead, this phase falls in a long paragraph containing a subject clause followed by several modifying clauses separated by commas:

> **1**. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

Ex. 2, '590 Patent, cl 1. The claims also contain no indentation or formatting to help a POSA understand what portion of the claim is intended to be modified by each of the modifying clauses. *See e.g.*, 37 CFR §1.75(i) ("Where a claim sets forth a plurality of elements or steps, each element or step of the claim should be separated by a line indentation."); *see also* MPEP 608.01(a) at ¶6.02(i) ("There may be plural indentations to further segregate subcombinations or related steps."). For the "wherein" clauses, the claims of the UWA Patents remedy this issue by

specifically identifying the element that each wherein clause modifies—*i.e.*, "the base sequence" or "the antisense oligonucleotide." But, for the disputed phrase, "in which uracil bases are thymine bases," there is no identification of the element the clause it intended to modify, and no way for a POSA to determine the meaning of the clause with reasonable certainty.

The ambiguity related to the phrase "in which uracil bases are thymine bases" leads to at least two equally likely interpretations:

- the phrase modifies the term "antisense oligonucleotide" as a whole, such that no uracil bases are included anywhere in the "antisense oligonucleotide;" or
- the phrase modifies the sequence of bases immediately preceding it (*e.g.*, SEQ ID NO: 195), such that the at least 12 consecutive bases of SEQ ID NO: 195 includes thymine bases in place of uracil bases.

Because a POSA has no way to determine which of these constructions are correct, it is impossible for a POSA to determine whether an oligonucleotide that has thymine bases in place of uracil bases within the "at least 12 consecutive bases" of SEQ ID NO: 195 or whether the oligonucleotide could include uracil bases elsewhere in the oligonucleotide. *See e.g.*, Ex. 43 ¶103 (providing examples). For this reason, the claims of the UWA Patents are indefinite because the appropriate claim scope cannot be determined. *See Teva*, 789 F.3d at 1341; *Vaxcel*, 2021 U.S. Dist. LEXIS 224684 at *6, *14.

This concern about claim scope is not simply an academic exercise without practical implications. Rather, as Dr. Hastings explains, researchers have created oligonucleotides that include both uracil and thymine bases at different positions in the oligonucleotide. *See* Ex. 43 ¶¶99-104. The use of both uracil and thymine bases may allow the oligonucleotide to improve its binding affinity—the exact reason that the UWA Patents describe for making base substitutions or modifications to the claimed oligonucleotides. *Id.* ¶115; '851 Patent 27:37-39.

As explained in detail below, the claims, specification, and prosecution history, fail to inform a POSA which of the at least two possible claim interpretations should be used, leading to a lack of reasonable certainty regarding claim scope, rendering the claims indefinite. *Teva*, 789 F.3d at 1341.

a. The Language and Structure of the Claims Does Not Inform a POSA as to Which Construction Is Appropriate

Courts "begin a claim construction analysis by considering the language of the claims themselves." *Trs. of Columbia Univ. v. Symantec Corp.*, 811 F.3d 1359, 1362 (Fed. Cir. 2016). Here, the language of the claims does not clarify which construction should be used. As Sarepta suggests, a POSA could reformat the claim language using indentation to try to understand how to interpret the claims. *See* Br. 42. But, there is more than one way to reformat the claims at issue:

1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA,	1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA,
wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195),	wherein **the base sequence** comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), **in which** uracil bases are thymine bases,
in which uracil bases are thymine bases,	
wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and	wherein **the antisense oligonucleotide** is a morpholino antisense oligonucleotide, and
wherein the antisense oligonucleotide induces exon 53 skipping;	wherein **the antisense oligonucleotide** induces exon 53 skipping;
or a pharmaceutically acceptable salt thereof.	or a pharmaceutically acceptable salt thereof.

'590 Patent, cl. 1 (left annotations suggested by Sarepta (Br. 43); right side—annotations suggested by Dr. Hastings (Ex. 43 ¶123)). The specific language of the claims supports each of these reformatted claims. As Sarepta argues, the comma before the "in which" phrase could support an

understanding that the "in which" phrase modifies the "antisense oligonucleotide" whole. Br. 42-43.[12]

However, the comma is also appropriate if the "in which" phrase modifies the preceding noun (*e.g.*, the listing of bases of SEQ ID NO: 195). When modifying the listing of bases of SEQ ID NO: 195, the "in which" phrase is, from a grammatical perspective, a "non-restrictive clause." *See* Ex. 46. Since the "in which" clause, when it modifies the listing of bases, is a "non-restrictive" clause from a grammatical perspective, it is required to be set apart by commas. *Id.* Accordingly, the existence of the comma does not clarify which interpretation is appropriate.

While Sarepta argues that its understanding of the term as modifying "antisense oligonucleotide" as a whole is the only correct interpretation, there are additional reasons to suggest that the "in which" phrase should modify the only preceding listing of bases instead. First, the other modifying phrases each begin with "wherein," while the disputed phrase begins with "in which." This suggests that the disputed phrase is different from the "wherein" clauses and should modify the immediately preceding claim language. *See* Ex. 43 ¶125. Second, the "wherein" clauses each specifically identify a previously identified subject to modify ("the base sequence" or "the antisense oligonucleotide"), but the "in which" clause does not—further suggesting it is modifying the immediately preceding language. *Id.* Third, the "in which" clause uses language that suggests that pre-existing "uracil bases" should be changed into "thymine bases." *Id.* ¶126. This language makes more sense if it refers to the specific listing of bases of SEQ ID NO: 195,

[12] Sarepta' citation to *Finisar* is inapplicable. Br. 43. In *Finisar* the Court determined if a modifier should be applied to ***all*** of the antecedents in a series or ***only the last*** antecedent. *Finisar Corp. v. DirectTV Grp., Inc.*, 523 F.3d 1323, 1336 (Fed. Cir. 2008). Here, there is no "series" of antecedents. Instead, the UWA Patents include a series of modifying clauses, and the Court must determine what the middle modifying clause should modify when the subject is not specified.

which actually expressly recites uracil bases that should be changed into thymine bases. *Id.* ¶¶126-128.

Thus, the specific language of the claim demonstrates that the phrase "in which uracil bases are thymine bases" is ambiguous at best. However, in contrast with the "wherein" limitations, the claim language slightly more strongly supports an interpretation that the phrase "in which uracil bases are thymine bases" modifies the listing of SEQ ID NO: 195 rather than the "antisense oligonucleotide" as a whole.

b. The Specification Supports Both Constructions

Claims must also "be read in view of the specification, of which they are a part." *Columbia*, 811 F.3d at 1362. Sarepta has argued that the specification of the UWA Patents supports its interpretation because it does not allow for "a mixture of uracil and thymine bases"—such that the "in which" phrase must modify the antisense oligonucleotide as a whole to ensure that only thymine bases are included. Br. 46. However, the specification of the UWA Patents teaches that base substitutions (like substituting uracil for thymine) can be made at individual bases in an oligonucleotide—confirming that oligonucleotides can have mixtures of thymine and uracil bases. *See e.g.,* '851 Patent 27:60-64, Table 1A. Due to this teaching, the specification of the UWA Patents does not clarify which of the two potential interpretations of the phrase "in which uracil bases are thymine bases" should be adopted.

As Sarepta correctly notes, the examples in the UWA Patents list oligonucleotides with only uracil bases—not a mixture:

TABLE 1A

Description of 2'-O-methyl phosphorothioate antisense oligonucleotides that have been used to study induced exon skipping during the processing of the dystrophin pre-mRNA. Since these 2'-O-methyl antisense oligonucleotides are more RNA- like, U represents uracil. With other antisense chemistries such as peptide nucleic acids or morpholinos, these U bases may be shown as "T".

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
1	H8A(-06+18)	GAU AGG UGG UAU CAA CAU CUG UAA
2	H8A (-03+18)	GAU AGG UGG UAU CAA CAU CUG
3	H8A(-07+18)	GAU AGG UGG UAU CAA CAU CUG UAA G
4	H8A(-06+14)	GGU GGU AUC AAC AUC UGU AA
5	H8A(-10+10)	GUA UCA ACA UCU GUA AGC AC

Id. However, these oligonucleotides are examples only, and "it is improper to read limitations from a preferred embodiment…into the claims." *GE Lighting Sols., LLC v. AgiLight, Inc.*, 750 F.3d 1304, 1308-10 (Fed. Cir. 2014); *see also Jang v. Bos. Sci. Corp.*, 493 F. App'x 70, 77 (Fed. Cir. 2012) ("[T]he district court impermissibly imported the…limitation into the claims based on the examples in the specification.").

The specification of the UWA Patents also specifically notes that "[o]ligonucleotides may also include nucleobase (often referred to in the art simply as 'base') modifications or substitutions." '851 Patent 27:35-37. One such substitution is replacing uracil bases with thymine bases for morpholino oligonucleotides. *Id.* at Table 1A. However, such substitution is not ***mandated*** by the UWA Patents—instead, Table 1A states that the uracil bases "***may be***" substituted. *Id.*; Ex. 43 ¶133. In addition, the specification of the UWA Patents teaches that "[i]t is not necessary [for] all positions in a given compound to be uniformly modified, and…the aforementioned modifications [including nucleobase modifications or substitutions] may be incorporated…at a single nucleoside within an oligonucleotide." '851 Patent 27:60-64. As explained by Dr. Hastings, the combination of teachings in the UWA Patents would lead a POSA

to understand that "(i) the nucleobases of morpholino antisense oligonucleotides could be modified such that the antisense oligonucleotides included thymine bases rather than uracil bases, and (ii) such modifications could be made on specific portions of a morpholino antisense oligonucleotide, such that the antisense oligonucleotide would include both thymine bases and uracil bases as part of the molecule." Ex. 43 ¶136. Since the specification of the UWA Patents teaches that oligonucleotides can contain a mixture of uracil and thymine bases, it does not provide any clarity as to the correct interpretation of the disputed phrase.

c. The Prosecution History Does Not Resolve the Ambiguity

In determining the meaning of claim terms, "[a] court should also consider the patent's prosecution history." *Columbia*, 811 F.3d at 1362-63. Here, Sarepta argues that the prosecution history of an abandoned parent application supports its interpretation of the "in which" phrase. Br. 43-45. However, the prosecution history identified by Sarepta does not inform a POSA as to claim scope with reasonable certainty.

Sarepta identifies two portions of the same Office Action Response in support of its arguments:

> Specifically, the pending claims are drawn to an antisense oligonucleotide having the following elements: (i) 25 bases comprising a base sequence that is 100% complementary to 25 consecutive bases of exon 53 of the human dystrophin pre-mRNA; (ii) 20 consecutive bases of SEQ ID NO: 193; (iii) uracil bases are thymine bases; (iv) the antisense oligonucleotide is a morpholino; (v) the antisense oligonucleotide induces exon 53 skipping; ***and*** (vi) the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

Ex. 20 at SRPT-VYDS-0094179.

> Further, none of the cited references teach or suggest combining the elements to result in the claimed antisense oligonucleotide. Specifically, there is no teaching or suggestion to generate an antisense oligonucleotide of 25 bases, wherein the antisense oligonucleotide comprises 20 consecutive bases of SEQ ID NO: 193, **and** wherein uracil bases are thymine bases, **and** wherein the antisense oligonucleotide is a morpholino, **and** wherein the resulting antisense oligonucleotide induces exon 53 skipping of the human dystrophin pre-mRNA.

Id. at SRPT-VYDS-0094181.

However, nothing in this Response discusses or evaluates whether the phrase "in which uracil bases are thymine bases" modifies (i) the oligonucleotide as a whole or (ii) the listing of bases immediately preceding the phrase, in this example, SEQ ID NO: 193. *See* Ex. 20 at SRPT-VYDS-0094177–85. Instead, the applicants' argument was focused on whether the prior art disclosed substituting uracil bases with thymine bases ***at all***—and did not focus on the specific location of the substitution. *Id.* at SRPT-VYDS-0094180 ("Applicants wish to point out that there is absolutely nothing in [the prior art reference] about substituting uracil bases…with thymine bases. In fact, the word 'thymine' (or its structure) is not described anywhere."). The listing of claim elements identified by Sarepta was simply intended to set out all of the elements of the claim—it was not intended to clarify the subject matter that the "in which" clause should modify. Ex. 43 ¶141. Accordingly, a POSA would not have read the listing of claim elements as specifying that the "in which" clause was intended to modify "antisense oligonucleotide" as a whole.

Moreover, the grammatical structure of the lists further confirms that a POSA would be unable to ascribe any clear meaning to the prosecution history identified by Sarepta. Specifically, the listed elements do not have the "parallel structure" that is typical of ordered lists of items. Ex. 42. Indeed, like the claims themselves, certain of the items specifically refer to the "antisense oligonucleotide" as the subject of the item (underlined in red, below), while the uracil bases item includes a different structure (underlined in blue, below).

> Specifically, the pending claims are drawn to an antisense oligonucleotide having the following elements: (i) 25 bases comprising a base sequence that is 100% complementary to 25 consecutive bases of exon 53 of the human dystrophin pre-mRNA; (ii) 20 consecutive bases of SEQ ID NO: 193; (iii) uracil bases are thymine bases; (iv) the antisense oligonucleotide is a morpholino; (v) the antisense oligonucleotide induces exon 53 skipping; ***and*** (vi) the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

Ex. 20 at SRPT-VYDS-0094179 (annotations added).

> Further, none of the cited references teach or suggest combining the elements to result in the claimed antisense oligonucleotide. Specifically, there is no teaching or suggestion to generate an antisense oligonucleotide of 25 bases, wherein the antisense oligonucleotide comprises 20 consecutive bases of SEQ ID NO: 193, **and** wherein uracil bases are thymine bases, **and** wherein the antisense oligonucleotide is a morpholino, **and** wherein the resulting antisense oligonucleotide induces exon 53 skipping of the human dystrophin pre-mRNA.

Id. at SRPT-VYDS-0094181 (annotations added). Given the inconsistent grammatical structure, a POSA would have difficulty determining whether the applicant actually intended the phrase to modify the "antisense oligonucleotide" as a whole, or whether the phrase was intended to modify "SEQ ID NO: 193" that immediately precedes the phrase in both lists. Ex. 43 ¶¶142-143.

Overall, the prosecution history fails to resolve the indefiniteness of the "in which" phrase. Even if the prosecution history slightly more strongly supports an interpretation that the phrase "in which uracil bases are thymine bases" modifies the "antisense oligonucleotide" as a whole, it is balanced by the language of the claim itself, which slightly more strongly supports an interpretation that the phrase modifies the listing of SEQ ID NO: 195. *See HTC Corp. v. IPCom GmbH & Co., KG*, 667 F.3d 1270, 1276 (Fed. Cir. 2012) ("Claim language and the specification generally carry greater weight than the prosecution history…[and the prosecution history] is less useful for claim construction purposes.").

d. A POSA Would Have Been Unable to Determine Claim Scope with Reasonable Certainty

A POSA, viewing the claims in the entirety of the intrinsic evidence, would have been unable to determine the appropriate construction of the phrase "in which uracil bases are thymine bases," rendering the claims of the UWA Patents indefinite. *Teva*, 789 F.3d at 1341; *Vaxcel*, 2021 U.S. Dist. LEXIS 224684 at *6, *14. Indeed, a POSA would have understood that "typical" oligonucleotides might contain only uracil bases or thymine bases. *See* Br. 45-46 (arguing about

"how researchers ***typically*** design antisense oligonucleotides" or how "researchers ***generally*** use either uracil bases or thymine bases" (emphasis added)). However, a POSA would also have understood that the UWA Patents teachings support oligonucleotides containing both uracil and thymine bases, and that such mixed oligonucleotides were being studied and researched for potential applications. *See* Ex. 43 ¶¶106-116. Accordingly, a POSA would have known that each of the two identified constructions of the "in which" phrase could be used and a POSA would not have been able to determine which construction should be used—rendering the claims of the UWA Patents indefinite.

3. Sarepta's Reply Position

NS acknowledges that Sarepta's construction of the thymine bases phrase—i.e., using thymine bases instead of uracil bases throughout the antisense oligonucleotide—is a "likely" interpretation. *See* Br. 48. But NS argues that the phrase is indefinite because a skilled artisan *could* conclude that it modifies the "12 consecutive bases" of SEQ ID: 195—allowing the antisense oligonucleotide to contain mixtures of thymines and uracils. *Id.*

NS again applies the wrong legal standard: two possible interpretations of differing scope do not establish indefiniteness. *See Nevro*, 955 F.3d at 41; *Nautilus*, 572 U.S. at 909. Further, NS's indefiniteness theory is again a hypothetical exercise: NS's Viltepso® product infringes the claims because it contains thymine bases throughout (Sarepta's construction), *including* in the portion derived from SEQ ID NO: 195 (NS's alternative). Stein Rep. Decl. ¶¶71-72. NS's speculation is not clear and convincing evidence of indefiniteness. *See Bristol-Meyers*, 2013 WL 12322088, at *13. Regardless, as discussed below, a skilled artisan would have understood the term to refer to the claimed antisense oligonucleotide as a whole. Br. 42-46.

Claims: Sarepta's construction is consistent with the structure and syntax of the claims, which use commas to set off each "wherein" and "in which" clause, indicating that the thymine

bases phrase modifies the claimed antisense oligonucleotide. NS has reformatted the claims to suggest that the "in which" clause modifies SEQ ID NO: 195:

Sarepta's Formatting	NS's Formatting
1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, **wherein** the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), **in which** uracil bases are thymine bases, **wherein** the antisense oligonucleotide is a morpholino antisense oligonucleotide, and **wherein** the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.	1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, **wherein the base sequence** comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), **in which** uracil bases are thymine bases, **wherein the antisense oligonucleotide** is a morpholino antisense oligonucleotide, and **wherein the antisense oligonucleotide** induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

See Br. 49-50.

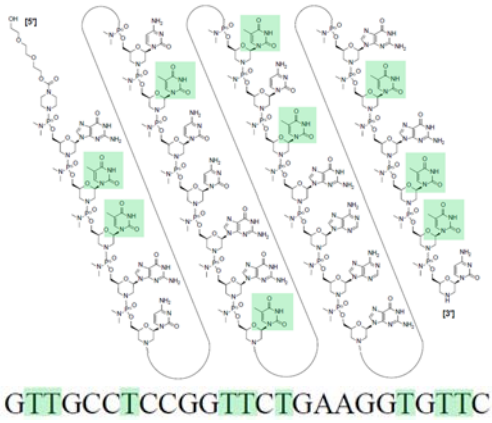
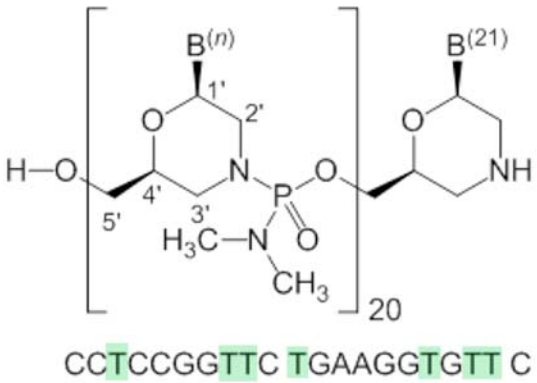
Regardless of formatting, NS provides no reasonable basis for treating the thymine bases phrase differently than the "wherein" clauses. Stein Rep. Decl. ¶¶46-50. NS first argues that the comma before the "in which" clause suggests that the phrase modifies the preceding noun, SEQ ID NO: 195. Br. 50. But context matters: the claims do not use one comma before the "in which" clause; they use *serial* commas before *every* "wherein" and "in which" clause. Grammatically, serial commas signify a listing of individual, independent items in a series. Ex. 52 ("Items in a series are normally separated by commas."). The serial nature of the language is reinforced by the Oxford comma separating the last two "wherein" clauses. *Id.* (an Oxford comma should be used before a conjunction joining the last two elements in a *series* of three or more). The claim's use

of serial commas reinforces that the "wherein" and "in which" clauses are independent, each modifying the claimed antisense oligonucleotide.[13]

NS also points out that the thymine bases phrase uses "in which" instead of "wherein." Br. 50. But these are known synonyms; for example, Webster's Dictionary defines "wherein" as "in which." *See* Ex. 51 at 1488. Further, the applicant and the Examiner used the terms interchangeably during prosecution, indicating that the thymine bases phrase similarly modifies the antisense oligonucleotide as a whole. *See, e.g.*, Ex. 20 at SRPT-VYDS-0094154-55, SRPT-VYDS-0094181 ("wherein uracil bases are thymine bases"); Stein Rep. Decl. ¶51.

NS contends that, in contrast to the "wherein" clauses, the thymine bases phrase does not set forth a previously identified subject to modify. Br. 50. But the phrase must be read in "the context of the claim as a whole." *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1347 (Fed. Cir. 2008); Stein Rep. Decl. ¶52. Here, the claims are directed to an "antisense oligonucleotide," which was exemplified in the specification and prior art to have either uracils or thymines, not mixtures of both. Br. 43-44, 45-46. Further, the claims are directed to "morpholino" antisense oligonucleotides, which typically contain thymines rather than uracils. *See* Ex. 38 at 6:19–26; Stein Rep. Decl. ¶67. For example, both golodirsen (Sarepta's morpholino product) and viltolarsen (NS's morpholino product) contain thymines rather than uracils:

[13] NS contends that *Finisar* involved a series of antecedents rather than a series of modifying clauses. Br. 50 n.12. That is a distinction without a difference. Here the issue is whether the claimed antisense oligonucleotide (the first antecedent in the claims) or SEQ ID NO: 195 (a subsequent antecedent, which itself modifies the first antecedent) should be modified by the thymine bases phrase. As in *Finisar*, the thymine bases phrase is set off by a comma from both, and thus, "should be read to apply to each of those antecedents." *Finisar*, 523 F.3d at 1336-37.

Golodirsen Sequence (Ex. 15 at §11)	Viltolarsen Sequence (Ex. 31 at §11)
	

NS further argues that the thymine bases phrase signals that it refers to the bases of SEQ ID NO: 195 because that sequence includes uracils. Br. 50-51. Again, however, the phrase is separated from SEQ ID NO: 195 by a comma. Had it been modifying that clause only, there would have been no need to include that comma. Stein Rep. Decl. ¶¶53-54. A skilled artisan would understand that the thymine bases phrase modifies the claimed antisense oligonucleotide as a whole. Br. 42-43; *see LBS Innovations L.L.C. v. Aaron Bros., Inc.*, C.A. No. 2:11-CV-142, 2012 WL 1492330, at *18-19 (E.D. Tex. Feb. 14, 2012) (construing an "in which" clause to modify the same subject as a preceding "whereby" clause).

Specification and Prosecution History: NS acknowledges that none of the exemplified antisense oligonucleotides in the specification use mixtures of uracils and thymines. Br. 51-52. While NS contends that Sarepta's construction reads limitations from these embodiments into the claims, the claims *already* include a limitation requiring the use of thymine bases in place of uracil bases. Ex. 1 at claim 1. That the specification also contemplates using different modifications in a single antisense oligonucleotide (Br. 52-53) is irrelevant, as claims should not be interpreted in contravention to their plain meaning. *August Tech. Corp. v. Camtek, Ltd.*, 655 F.3d 1278, 1285

(Fed. Cir. 2011) (the existence of an embodiment not encompassed by a claim construction "does not outweigh" the claim language); *see* Stein Rep. Decl. ¶¶55-57.

The prosecution history further establishes that the thymine bases phrase should apply to the antisense oligonucleotide as a whole. Br. 44-45. In distinguishing structurally identical claims from the prior art, the applicant identified "uracil bases [being] thymine bases" as a feature of the claimed *antisense oligonucleotide*. *Id.* Indeed, multiple prosecution statements do so. *E.g.*, Ex. 20 at SRPT-VYDS-0094179 ("the pending claims are drawn to an *antisense oligonucleotide* having the following elements: . . . (iii) uracil bases are thymine bases"); *id.* at SRPV-VYDS-0094181 ("an *antisense oligonucleotide* . . . wherein uracil bases are thymine bases"); *id.* at SRPT-VYDS-0094154-55 (Examiner stating the claims are drawn to "an *antisense oligonucleotide* . . . wherein uracil bases are thymine bases").

NS argues that the listed claim elements "do not have the 'parallel structure' that is typical of ordered lists of items." Br. 54-55. But, as illustrated below, the applicant labeled the listed elements using sequential roman numerals (in green) *and* signified the independent nature of each listed element using the phrase, "and wherein" (in pink). Stein Rep. Decl. ¶¶58-60.

> Specifically, the pending claims are drawn to an antisense oligonucleotide having the following elements: (i) 25 bases comprising a base sequence that is 100% complementary to 25 consecutive bases of exon 53 of the human dystrophin pre-mRNA; (ii) 20 consecutive bases of SEQ ID NO: 193; (iii) uracil bases are thymine bases; (iv) the antisense oligonucleotide is a morpholino; (v) the antisense oligonucleotide induces exon 53 skipping; ***and*** (vi) the antisense oligonucleotide is chemically linked to a polyethylene glycol chain.

Ex. 20 at SRPT-VYDS-0094179.

> Further, none of the cited references teach or suggest combining the elements to result in the claimed antisense oligonucleotide. Specifically, there is no teaching or suggestion to generate an antisense oligonucleotide of 25 bases, wherein the antisense oligonucleotide comprises 20 consecutive bases of SEQ ID NO: 193, **and** wherein uracil bases are thymine bases, **and** wherein the antisense oligonucleotide is a morpholino, **and** wherein the resulting antisense oligonucleotide induces exon 53 skipping of the human dystrophin pre-mRNA.

Id. at SRPV-VYDS-0094181.

The applicant's treatment of these claim elements underscores that each listed element, including "uracil bases are thymine bases," independently modifies the claimed antisense oligonucleotide as a whole.

Extrinsic Evidence: Sarepta's construction is consistent with common practice: researchers typically included either uracils or thymines, but not both, in a single antisense oligonucleotide. Stein Decl. ¶¶80-83. Indeed, NS's expert did not identify any prior art antisense oligonucleotide containing both uracils and thymines. Hastings Decl. ¶¶106-116 (citing Exs. 24, 38-41); Stein Rep. Decl. ¶¶61-70. Many of the references relied on by NS were published after the UWA patents were filed. *Nautilus*, 572 U.S. at 908. Others indicate that thymine bases can be used in place of uracil bases, without suggesting they can be mixed in a single oligonucleotide. NS's cited prior art reference depicts an antisense oligonucleotide using only one type of base (uracils), not a mixture of different types of bases. *See* Ex. 24 at 190.

4. Nippon's Sur-Reply Position

Sarepta mischaracterizes NS's arguments with respect to Term 3 and fails to address the issues that cause a POSA to lack reasonable certainty regarding claim scope. First, Sarepta argues that "two possible interpretations of differing scope do not establish indefiniteness." Br. 56. Yet, this is not what NS argued. NS demonstrated that "a POSA has no way to choose between the proposed constructions," resulting in a "'classic' situation" of indefiniteness. *Vaxcel*, 2021 U.S.

Dist. LEXIS 224684, at *14; Br. 47-56. Second, Sarepta claims that "NS's indefiniteness theory is…a hypothetical exercise" because NS's accused product infringes under either construction. Br. 56. But, "[t]he test for indefiniteness does not depend on…the nature of [the] accused product to determine infringement, but instead on whether the claim delineates to a skilled artisan the bounds of the invention." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1340-41 (Fed. Cir. 2005).

Here, the claims at issue include long paragraphs without indentation:

> 1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA, wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), in which uracil bases are thymine bases, wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and wherein the antisense oligonucleotide induces exon 53 skipping; or a pharmaceutically acceptable salt thereof.

Ex. 2, cl 1. This structure leads to two potential constructions—(i) Term 3 requires that the "antisense oligonucleotide" has only thymine (not uracil) bases or (ii) Term 3 requires that the uracil bases in SEQ ID NO: 195 are thymine bases:

1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA,	1. An antisense oligonucleotide of 20 to 31 bases comprising a base sequence that is 100% complementary to consecutive bases of a target region of exon 53 of the human dystrophin pre-mRNA,
wherein the base sequence comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195),	**wherein the base sequence** comprises at least 12 consecutive bases of CUG AAG GUG UUC UUG UAC UUC AUC C (SEQ ID NO: 195), **in which** uracil bases are thymine bases,
in which uracil bases are thymine bases,	
wherein the antisense oligonucleotide is a morpholino antisense oligonucleotide, and	**wherein the antisense oligonucleotide** is a morpholino antisense oligonucleotide, and
wherein the antisense oligonucleotide induces exon 53 skipping;	**wherein the antisense oligonucleotide** induces exon 53 skipping;
or a pharmaceutically acceptable salt thereof.	or a pharmaceutically acceptable salt thereof.

These differing constructions render uncertain whether an antisense oligonucleotide with uracil bases outside the 12 consecutive bases of SEQ ID NO: 195 can infringe. *Id.* at 25-26. The claims, specification, prosecution history, and extrinsic evidence all fail to inform a POSA which of the possible claim interpretations should be used, rendering the claims indefinite. *Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 789 F.3d 1335, 1341 (Fed. Cir. 2015).

C. Term 2: "the target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69)"

Sarepta's Proposed Construction	NS's Proposed Construction
Not indefinite Sarepta proposes construing the phrase as: "the target region is within nucleotides +23 to +69 of exon 53 of the human dystrophin pre-mRNA"	*Indefinite*

1. Sarepta's Opening Position

a. The Annealing Site Phrase Specifies That the Target Region Is Within Nucleotides +23 to +69 of Exon 53 of the Human Dystrophin Pre-mRNA

The annealing site phrase only appears in the claims of the '851 patent. The intrinsic and extrinsic evidence—including NS's admissions—support Sarepta's construction that the claimed target region is within nucleotides +23 to +69 of exon 53 of the human dystrophin pre-mRNA. Stein Decl. ¶85.

The claims recite that the target region of the claimed antisense oligonucleotide is within two annealing sites, "H53A(+23+47)" and "H53A(+39+69)." The specification describes how to interpret these annealing sites. Ex. 1 at 22:41-65. It explains that a "target region" is expressed in the format of "H#A/D(x:y)"—"H" designating the species, "#" designating the target dystrophin exon, and "A/D" identifying the beginning (the 5'-end) or the end (the 3'-end) of the exon, and "(x:y)" representing the annealing coordinates. *Id.* The specification incorporates the

nomenclature system reported in the prior art, which uses four identifiers to define the region of the pre-mRNA targeted by an antisense oligonucleotide: **Letter** / **Number** / **A or D** / **Coordinates**. Stein Decl. ¶¶86-87.

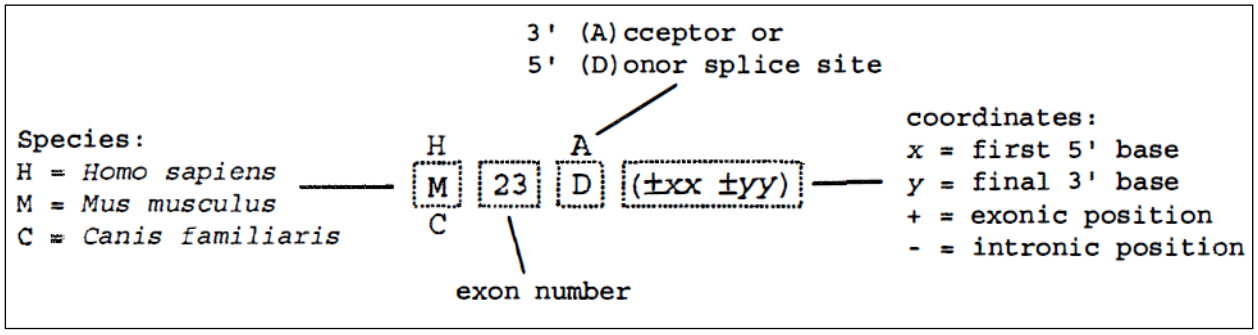


Figure 4. Nomenclature System for Exon-Skipping Antisense Oligonucleotides (Stein Decl. ¶41)

A skilled artisan familiar with this standard nomenclature would have understood that "H53A(+23+47)" and "H53A(+39+69)" corresponds to nucleotides +23 to +47 ("(23+47)") and nucleotides +39 to +69 ("(+39+69)"), respectively, each counted from the beginning ("A") of exon 53 ("53") of the human dystrophin pre-mRNA ("H"). Stein Decl. ¶88. A skilled artisan also would have understood that the claimed target region falls within a portion covered by the two annealing sites collectively, i.e., nucleotides **+23** to **+69** of exon 53 of the human dystrophin pre-mRNA—the beginning marked by one annealing site (H53(+**23**+47)) and the end marked by the other annealing site (H53A(+39+**69**)). *Id.*

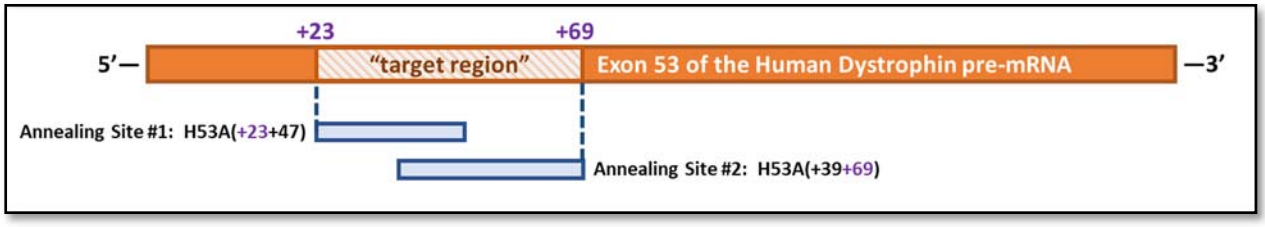


Figure 5. "Target Region" of the '851 Patent (Stein Decl. ¶88)

The annealing site claim language was addressed during prosecution of the '851 patent. Stein Decl. ¶89. In responding to an obviousness rejection, the applicant explained that the cited prior art did not render the claim features obvious, including "the exon 53 target region +23 to +69." Ex. 22 at SRPT-VYDS-0004786; *see Fenner Invs.*, 778 F.3d at 1323 ("[a]ny explanation, elaboration, or qualification presented by the inventor during patent examination is relevant" to claim construction). The applicant similarly explained during prosecution of the related '827 patent that the phrase "delineates a target region . . . spanning from, and including, endpoint H53A+23 to, and including endpoint H53A+69."[14] Ex. 23 at SRPT-VYDS-0006276-77; *see Capital Mach.*, 524 F. App'x at 649; Stein Decl. ¶89.

NS interpreted a nearly identical phrase as referring to the same region. Stein Decl. ¶¶90-91. In opposing the European counterpart of the Wilton patents, NS construed the phrase "annealing site H53A(+23+47), annealing site H53A(+39+69), or *both*." Ex. 11 at 4-5. According to NS, "both" meant that the target region fell within "the area from nucleotide +23 until +69." *Id.* NS's interpretation in that proceeding is consistent with Sarepta's proposed construction here.

b. The Claimed Target Region Is Not Indefinite

NS contends that "it is unclear what portion of H53A the 'target region' must be within" and the claimed target region is therefore indefinite. Ex. 36 at 26.

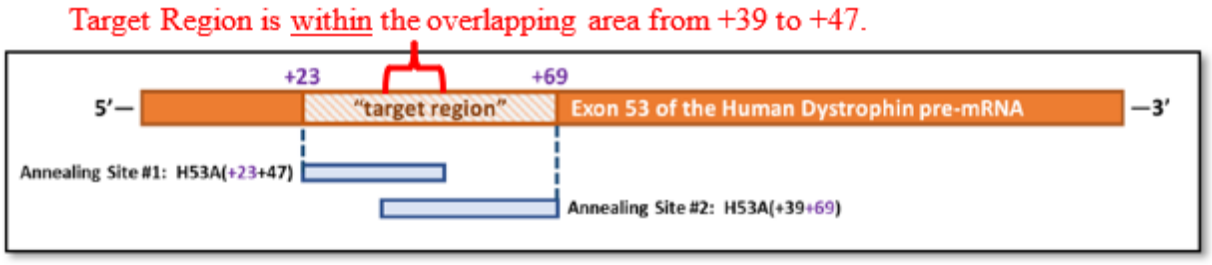
The claimed target region is not indefinite. Stein Decl. ¶92. As discussed above, the specification and prosecution history provide express guidance on how to interpret the claims, and a skilled artisan familiar with antisense oligonucleotide technology would have understood that the claimed target region is bookended by two annealing sites, H53A(+23+47) and H53A(+39+69). *See supra* § IV.C.1.a. Because the '851 patent informs, with reasonable certainty,

[14] Although the '827 patent ultimately issued without this phrase, the applicant's statements characterizing it are highly relevant. *See supra* note 11.

a skilled artisan about the scope of the invention, it satisfies the definiteness requirement. *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 901 (2014).

2. Nippon's Responsive Position

The disputed phrase recites that the "target region is within annealing site H53A(+23+47) and annealing site H53A(+39+69)." The plain and ordinary meaning of this phrase necessitates that the target region be "***within*** annealing site H53A(+23+47) ***and*** annealing site H53A(+39+69)." Two key words in this phrase are important for its construction—"within" and "and." "Within" is a common English word that the Merriam Webster Online Dictionary defines as "into the range of." Ex. 44. Thus, the "target region" must be "into the range of" the annealing site. The word "and" is a conjunctive limitation requiring both elements separated by "and" to be met. *See SuperGuide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 886 (Fed. Cir. 2004). Thus, the plain and ordinary meaning of the disputed phrase requires a "target region" that is both "***within*** annealing site H53A(+23+47)" ***and*** "[***within***] annealing site H53A(+39+69)." *Id.* (finding "at least one of [A, B, C,] and [D]" required that "the user select at least one value for each category."). A POSA would have understood that the "target region" of this claim is, at most, 9 nucleotides long (from +**39** to +**47**), because those are the only overlapping nucleotides that are "within" both annealing sites:



Ex. 43 ¶93.

Although this claim language is easily understood, it still renders the '851 Patent's claims indefinite because it is impossible for an "antisense oligonucleotide…comprising a base sequence [of] **at least 12 consecutive bases**" to be "100% complementary to consecutive nucleotides" of a "target region" that is **only 9 bases long**. *See Synchronoss Techs., Inc. v. Dropbox, Inc.*, 987 F.3d 1358, 1366-67 (Fed. Cir. 2021) (holding claims indefinite as the claims were "nonsensical and require[ed] an impossibility"); *Koki Holdings Co. v. Kyocera Senco Indus. Tools, Inc.*, No. CV 18-313-CFC, 2021 WL 1092579, at *2 (claims that "require a physical impossibility…are inherently unclear and cannot provide 'reasonable certainty about the scope of the invention'"). Indeed, this is precisely why an examiner rejected claims during the prosecution of the related '827 patent as indefinite. As the Examiner explained:

> The claims recite that the target region is "within" the two annealing sites H53A(+23+47) and H53A(+39+69). The target region within the annealing sites H53A(+23+47) and H53A(+39+69) is 9 base long (i.e., 47-39), whereas the claimed antisense molecule is 20 to 31 bases long and is 100 % complementary to consecutive nucleotides of the target region, and comprises at least 12 consecutive bases of the sequence of SEQ ID NO: 195. Because the target region within the two listed annealing sites is 9 base long, it is not clear how a 20 to 31 base oligonucleotide would be 100% complementary to consecutive nucleotides of the target region. Thus, the meets and bounds of the claimed antisense oligonucleotide is not clear.

Ex. 23 at SRPT-VYDS-0006254-255 (annotations added).

Different examiners made a similar rejection in related reissue Application No. 15/645,842 (which issued as RE47,691):

> The new claims 44-64 recite that the target region is "within" the two annealing sites H53A(+23+47) and H53A(+39+69). The target region within the annealing sites H53A(+23+47) and H53A(+39+69) is 9 base long (i.e., 47-39), whereas the claimed antisense molecule is 25 base long and is 100 % complementary to 25 consecutive nucleotides of the target region, and comprises at least 20 consecutive bases of the sequence of SEQ ID NO: 193. Since, the target region within the two listed annealing sites is 9 base long, it is not clear how 25 base oligonucleotide would be 100% complementary to 25 consecutive nucleotides of the target region. It is not clear whether the target region is within the two claimed annealing sites (which is 9 base long) or the antisense molecule anneals to only H53A(+39+69) since the claims also recite that the base sequence of the antisense molecule comprises at least 20 consecutive bases of sequence of SEQ ID NO: 193. Thus, meets and bounds of the claimed antisense molecule is not clear.

Ex. 45 at 15 (annotations added). While UWA attempted to challenge the examiners' determinations, it ultimately acquiesced to the rejections by deleting the disputed phrase. Ex. 23 at SRPT-VYDS-0006277; Ex. 45. UWA's acquiescence during prosecution of the related '827 Patent and '691 Reissue Patent supports NS's interpretation that the disputed phrase is indefinite.

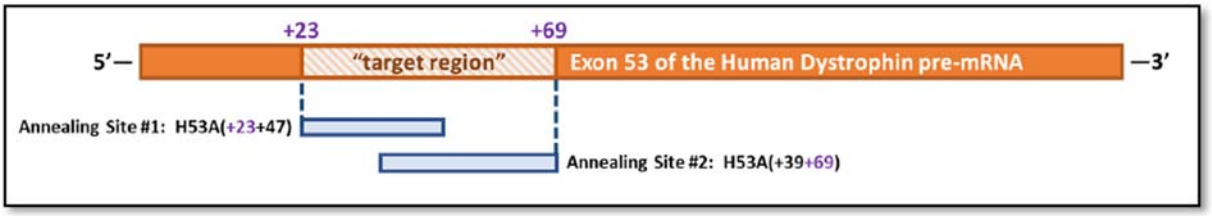
Sarepta argues that a person skilled in the art "would have understood that the claimed target region falls within a portion covered by the two annealing sites collectively, *i.e.*, nucleotides +23 to +69 of exon 53 of the human dystrophin pre-mRNA." Br. 64. But that is not what the claim recites. If UWA intended for the "target region" to be "within nucleotides +23 to +69 of exon 53 of the human dystrophin pre-mRNA," UWA could have easily used that express language in the claim. UWA did not and must now live with its chosen language. *Chef Am.*, 358 at 1374; *Koki Holdings*, 2021 WL 1092579, at *2 ("[I]t is improper to rewrite claim language to save a patent from impossibility.").

To support its construction, Sarepta wrongly relies on NS's opposition to "the European counterpart of the Wilton patents," during which "NS interpreted a nearly identical [(according to Sarepta)] phrase as referring to" nucleotides +23 until +69, "consistent with Sarepta's proposed construction here." Br. 65. But the phrase NS interpreted in the European Opposition was far

from "nearly identical" to the disputed phrase here. That phrase recited a target region "***designated as*** annealing site H53A (+23+47), annealing site H53A (+39+69), ***or*** both." Ex. 37 ¶90. Thus, instead of "within" and "and," the European counterpart used the phrase "designated as" and the conjunction "or." This difference in word choice gives the European counterpart a very different "target region" than the patents at issue here. *See Google LLC v. Sonos, Inc.*, No. C 20-06754, 2022 WL 17968767, at *1-*2 (N.D. Cal. 2022) (casting doubt on the relevance of statements made before the Australian Patent Office because "claim 1 of the Australian application … is ***not identical*** to claim 1 of the '033 patent."). Indeed, had the UWA Patents used the same language as the European counterpart, Sarepta's proposed construction here may be appropriate. But courts "construe the claim as written, not as the patentees wish they had written it." *Chef Am.*, 358 F.3d at 1374.

Additionally, while Sarepta's proposed construction requires "the target region" to be "within nucleotides +23 to +69 of exon 53 of the human dystrophin pre-mRNA," its arguments suggest that the "target region" is the *entire region* "spanning from nucleotides +23 to +69." *See, e.g.*, Br. 64-65 (referring to "'the exon 53 ***target region +23 to +69***'" and identifying "'a ***target region***…***spanning from***, and including, ***endpoint H53A+23*** to, and including ***endpoint H53A+69***'"), 19 ("[T]he claimed ***target region is bookended by two annealing sites, H53A(+23+47) and H53A(+39+69)***.'"). As Dr. Stein explains:

> [T]hese ***overlapping annealing sites define a target region*** within exon 53 of the human dystrophin pre-mRNA. Specifically, as illustrated below, ***these two annealing sites identify a region spanning from nucleotide +23 to nucleotide +69 of exon 53***.



Ex. 37 ¶¶88-89. Sarepta's confusion over its own position merely reinforces NS's point—the plain meaning of the '851 Patent's claims leads to indefiniteness, and impermissible judicial rewriting would be required to salvage their validity. *Synchronoss Techs.*, 987 F.3d at 1366-67; *Koki Holdings*, 2021 WL 1092579, at *2.

The plain language of the disputed term requires a "target region" that is, at most, nine bases long. Because the remaining claim limitations impossibly require a base sequence of at least 12 bases to be 100% complementary to consecutive bases of the target region, the claim is indefinite.

3. Sarepta's Reply Position

a. The Evidence Supports Sarepta's Construction

The claims state that the target region of the claimed antisense oligonucleotide is within two annealing sites, "H53A(+23+47)" and "H53A(+39+69)." Based on the specification's nomenclature, a skilled artisan would understand that the target region falls within a portion covered by the two annealing sites collectively, i.e., nucleotides +23 to +69 of exon 53. Stein Decl. ¶88; Stein Rep. Decl. ¶73. Consistent with this understanding, the applicant explained during prosecution that the prior art did not render "the exon 53 target region +23 to +69" obvious. Ex. 22 at SRPT-VYDS-0004786; Stein Rep. Decl. ¶74.

NS asserts that Sarepta's construction does not repeat "what the claim recites." Br. 68. But the purpose of claim construction is to explain how a skilled artisan would have understood the term, not to repeat it. *See Phillips.*, 415 F.3d at 1312-13. Here, a skilled artisan would have

understood that the target region is within nucleotides +23 to +69 of exon 53 of the human dystrophin pre-mRNA. *See* Br. 63-65.

NS also argues that the patentee could have written alternate language if it intended the target region to be within nucleotides +23 to +69. Br. 68. But a patentee is free to choose its own language in claiming an invention. *Thorner v. Sony Comput. Ent. Am. L.L.C.*, 669 F.3d 1362, 1367 (Fed. Cir. 2012). As explained during prosecution, the phrase "delineates a target region . . . spanning from, and including, endpoint H53A+23 to, and including endpoint H53A+69." *See* Br. 65; Ex. 23 at SRPT-VYDS-0006276-77.

NS cannot retreat from its prior statements supporting Sarepta's construction. *See* Br. 68-69. NS construed the phrase "annealing site H53A(+23+47), annealing site H53A(+39+69), or both" in opposing a European counterpart to the Wilton patents *See* Ex. 11 at 3. There, NS explained that "both" referred to "both annealing sites"—i.e., "the area from nucleotide +23 until +69." *Id.* at 4-5. Contrary to its current position, NS nowhere focused on, or even mentioned, use of the term "or." This "blatant admission by this same defendant before the [European Patent Office] clearly supports" Sarepta's construction. *See Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1374 (Fed. Cir. 2005).

b. NS's "Impossible" Construction Should Be Rejected

Instead of construing the claims as written, NS rewrites the disputed phrase to raise an indefiniteness challenge. NS argues that the phrase requires a target region that is "within annealing site H53A(+23+47) and ***within*** annealing site H53(+39+69)." Br. 66. According to NS, only the region from nucleotides +39 to +47 is "within" *both* annealing sites. *Id.*

Importantly, however, the second "within," bolded above, is not used in the claims. *See* Stein Rep. Decl. ¶¶75-76. NS alleges that "'and' is a conjunctive limitation requiring both elements separated by 'and' to be met." *Id.* The word "and," however, is context dependent and

can denote alternatives. *See, e.g.*, *Kaufman v. Microsoft Corp.*, 34 F.4th 1360, 1373 (Fed. Cir. 2022) ("in certain contexts, the word 'and' can reasonably be understood to denote alternatives, rather than conjunctive requirements"); *Ortho-McNeil Pharm., Inc. v. Mylan Lab'ys, Inc.*, 520 F.3d 1358, 1361-63 (Fed. Cir. 2008) (construing "and" to connote alternatives when a conjunctive meaning would lead to "nonsensical" results). This is clearly such a case, as NS's rewrite (1) impermissibly creates an "impossible" conflict with other claim language and (2) excludes the preferred embodiments from the claims.

A claim should be construed to "preserve its validity" when a reasonable construction is available. *Ruckus Wireless, Inc. v. Innovative Wireless Sols., L.L.C.*, 824 F.3d 999, 1004 (Fed. Cir. 2016); *Kaufman*, 34 F.4th at 1372-73. As NS acknowledges, its rewrite of the claim language would create a target region that is "***only*** 9 bases long" (from positions +39 to +47). Br. 66-67. But, as NS also acknowledges, the claims require that the target region is at least 12 nucleotides in length, since the antisense oligonucleotide contains "***at least*** 12 consecutive bases" that are 100% complementary to the target region. *Id.* at 67. This "impossible" conflict reinforces the impropriety of NS's construction. Stein Rep. Decl. ¶¶77-78. In contrast, Sarepta's proposed construction identifies a target region that is 47 bases long (from positions +23 to +69), consistent with the remaining claim language requiring "at least 12 consecutive bases" of SEQ ID NO: 195. *See Kaufman*, 34 F.4th at 1373.

NS's construction also excludes the preferred embodiments from the claim, which is "rarely, if ever correct." *Id.* at 1372. Indeed, under NS's construction, ***none*** of the antisense oligonucleotides disclosed in the specification would be covered by the claims. Stein Rep. Decl. ¶¶81-83. This nonsensical result highlights the untenability of NS's position. *Ortho-McNeil*,

520 F.3d at 1361-63 (the "nonsensical result" of excluding a preferred embodiment supports construing "and" as the patentees intended, i.e., connoting alternatives).[15]

NS cites no intrinsic evidence in the claims or specification to support its theory, instead pointing to select statements of the Examiner. *See* Br. 66-68; Hastings Decl. ¶¶94-95. These statements, however, do "not provide a sufficient reason to adopt a different construction from *the one clearly indicated by the rest of the prosecution history*." *Univ. of Mass. v. L'Oréal S.A.*, 36 F.4th 1374, 1384 (Fed. Cir. 2022). Indeed, the applicant repeatedly explained that the phrase covered nucleotides +23 to +69 of exon 53. Ex. 45 at 29-30 ("spanning from H53A+23 to H53A+69"); Ex. 22 at SRPT-VYDS-0004786 ("the exon 53 target region +23 to +69"); Ex. 23 at SRPT-VYDS-0006277 ("spanning from, and including, endpoint H53A+23 to, and including endpoint H53A+69"); Stein Rep. Decl. ¶¶79-80. NS cannot dismiss the applicant's clear statements merely because the phrase was deleted from the claims of other applications. "Any explanation, elaboration, or qualification presented by the [applicant] during patent examination *is relevant*" to claim construction. *Fenner*, 778 F.3d at 1323; *see Uship Intellectual Props., LLC. v. United States*, 714 F.3d 1311, 1315 (Fed. Cir. 2013) (prosecution history analysis "focuses on what the applicant said, not on whether the representation was necessary or persuasive").

The Court should reject NS's indefiniteness theory, which is premised on an "impossible" construction, and adopt Sarepta's construction.

4. Nippon's Sur-Reply Position

Sarepta's proposed construction rewrites the claim and ignores its plain and ordinary meaning. Here, as NS's position recognizes, the claim term at issue is "the target region is ***within***

[15] The sole case cited by NS to support its "conjunctive" construction is immaterial. Br. 66. In *SuperGuide*, the court accepted a construction of "and" as a conjunctive limitation in part because the intrinsic evidence contradicted the alternative construction. *See* 358 F.3d at 885-88. The opposite is true here.

annealing site H53A(+23+47) ***and*** annealing site H53A(+39+69)." The plain and ordinary meaning of "within" and "and" and requires that the target site be "***within*** annealing site H53A(+23+47) ***and within*** annealing site H53A(+39+69)." Br. 66-67. This provides an overlapping area that is 9 nucleotides long (from +39 to +47) as those are the only nucleotides "within" both annealing sites. This renders the claim indefinite because it establishes an impossibility with another limitation of the claim; a base sequence that is 100% complementary to a target region that is 9 bases long cannot also comprise 12 consecutive bases of SEQ ID NO: 195. *Synchronoss Techs., Inc. v. Dropbox, Inc.*, 987 F.3d 1358, 1366-67 (Fed. Cir. 2021).

Sarepta seeks to rewrite the claim to preserve its validity. But this Court must "construe the claim as written, not as the patentees wish they had written it," and cannot "rewrite claim language to save a patent from impossibility." *Chef Am., Inc. v. Lamb-Weston, Inc.*, 358 F.3d 1371, 1374-75 (Fed. Cir. 2004); *Koki Holdings Co. v. Kyocera Senco Indus. Tools, Inc.*, No. CV 18-313-CFC, 2021 WL 1092579 *2 (D. Del. Mar. 22, 2021).

Sarepta argues that the Court should read the word "and" as "denot[ing] alternatives." Br. 71-72 (citing *Kaufman v. Microsoft Corp.*, 34 F.4th 1360, 1373 (Fed. Cir. 2022) and *Ortho-McNeil Pharm., Inc. v. Mylan Lab'ys, Inc.*, 520 F.3d 1358, 1361-63 (Fed. Cir. 2008)). Yet, the cases Sarepta cites make clear that "and" is construed to denote alternatives when the claim "describe[s] two mutually exclusive possibilities…connected by the word 'and.'" *Kaufman*, 34 F.4th at 1373 (citing *Ortho-McNeil*, 520 F.3d at 1361). That is not the case here. Giving "and" its traditionally conjunctive meaning makes perfect sense and identifies a "target region" that is 9 bases long. This 9-base target region is consistent with the specification. Preferred embodiments, including SEQ ID NOS. 192 (+39+62), 193 (+39+69), and 195 (+23+47), all include a base sequence that is 9 bases long and is 100% complementary to the 9-base target region:

SEQ ID	SEQUENCE	NUCLEOTIDE SEQUENCE (5'-3')
192	H53A(+39+62)	CUG UUG CCU CCG GUU CUG AAG GUG
193	H53A(+39+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G
194	H53D(+14-07)	UAC UAA CCU UGG UUU CUG UGA
195	H53A(+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C

'851 Patent at Table 1A. The 9-base target region is also consistent with the prosecution history, as the examiner repeatedly identified the overlapping areas as the "target region" in related patents. Ex. 23 at SRPT-VYDS-0006254-255; Ex. 45 at 15; *Dolby Labs., Inc. v. Intertrust Techs. Corp.*, No. 19-cv-03371-EMC, 2021 U.S. Dist. LEXIS 20762, at *31 (N.D. Cal. Feb. 3, 2021) ("[S]tatements by an examiner that shed light on the examiner's understanding of the claim scope are probative in determining the proper scope of [a] claim."). While the applicant initially disagreed with the examiner and argued otherwise, it ultimately acquiesced to the examiner's understanding by deleting the disputed phrase. Ex. 23 at SRPT-VYDS-0006277; Ex. 45; Ex. 43 ¶95.

Sarepta's argument that NS's statements in opposing a related European counterpart support its position is incorrect. The language at issue in the European counterpart was a target region "designated as annealing site H53A (+23+47), annealing site H53A (+39+69), or both." Ex. 37 ¶90. Even ignoring the counterpart's use of "or," the counterpart states that the target region is "designated as" rather than "within" both sites. *Id.* This difference in word choice alone is critical. A POSA would have understood that a target region "within" both sites would only include the overlapping region—rendering the claim indefinite. *Google LLC v. Sonos, Inc.*, No. C 20-06754, 2022 WL 17968767, at *1-*2 (N.D. Cal. 2022).

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March 20, 2023